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(54) **BISPECIFIC ANTIBODY AND USE THEREOF**

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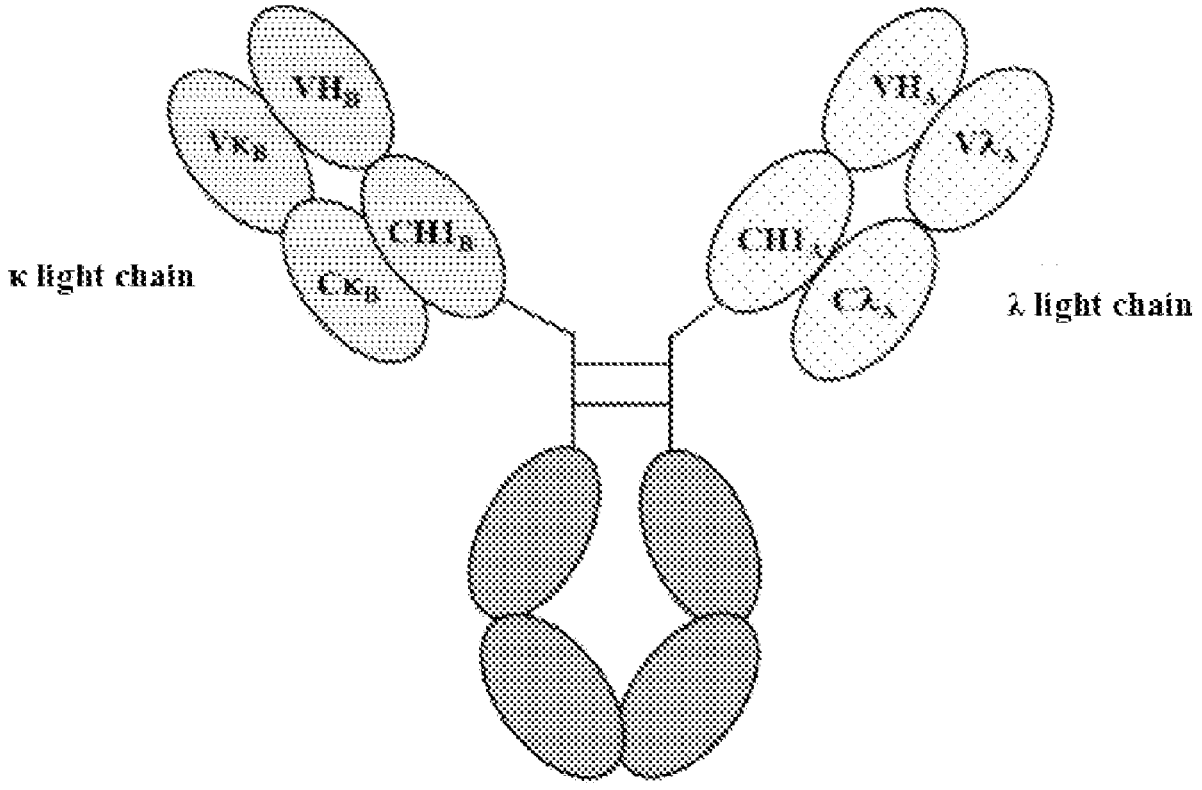
CPC ***C07K 16/468*** (2013.01); ***C12N 15/63*** (2013.01); *C07K 2317/31* (2013.01); *C07K 2317/565* (2013.01); *C07K 2317/52* (2013.01)

(57) **ABSTRACT**

Provided are a bispecific antibody or an antigen-binding fragment thereof, a nucleic acid encoding the same, a cell comprising the nucleic acid, a composition comprising the bispecific antibody or antigen-binding fragment thereof, the nucleic acid and/or the cell, and related applications of the bispecific antibody or antigen-binding fragment thereof in the treatment of cancer.

Specification includes a Sequence Listing.



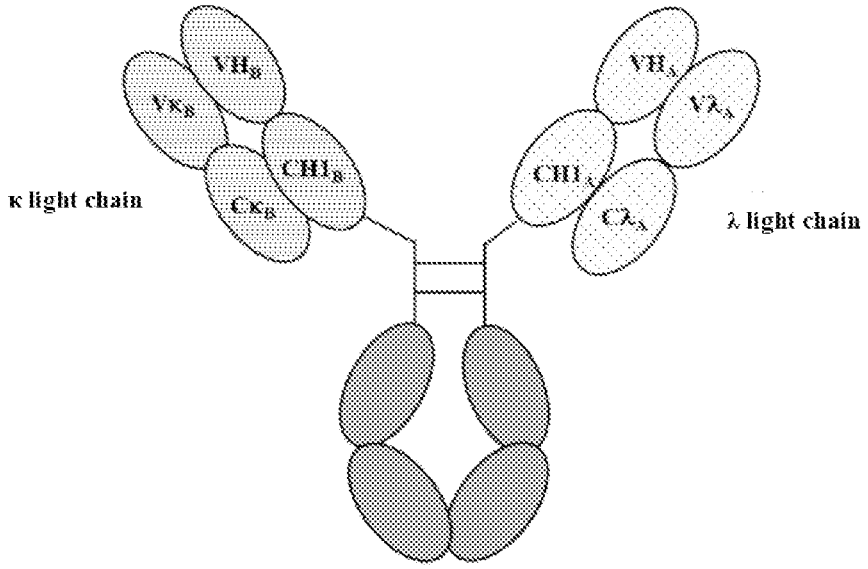


Figure 1

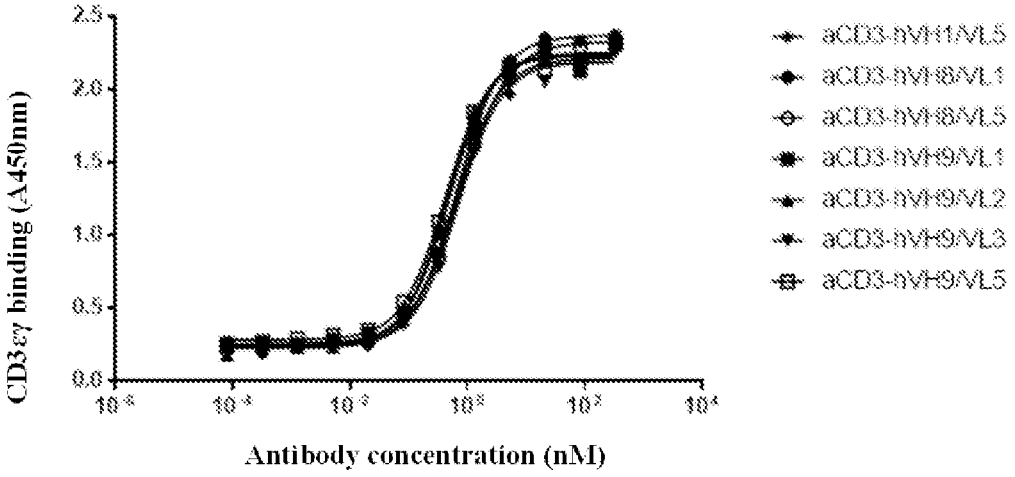


Figure 2

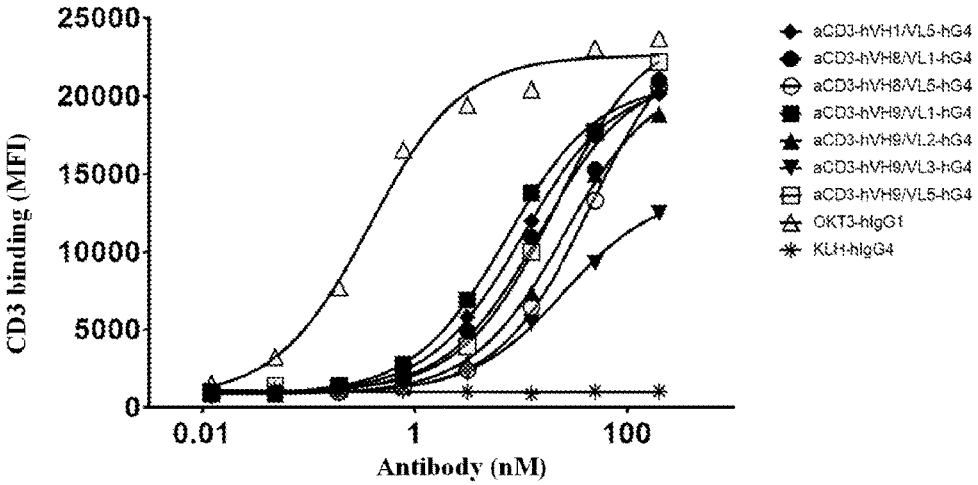


Figure 3

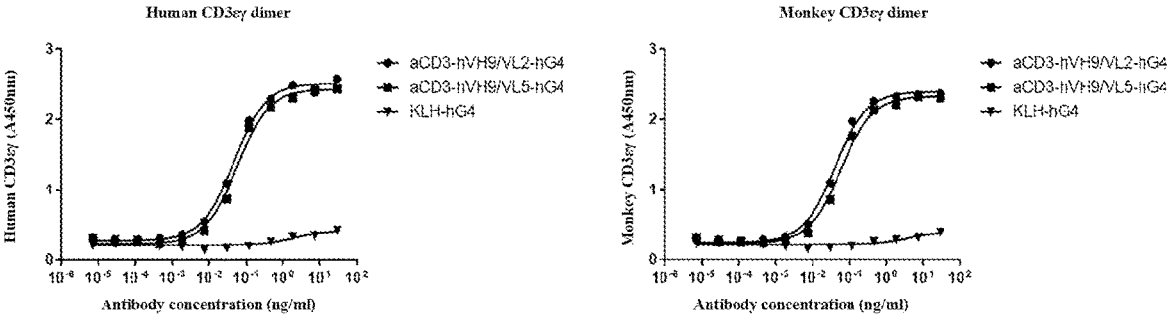


Figure 4

Figure 5

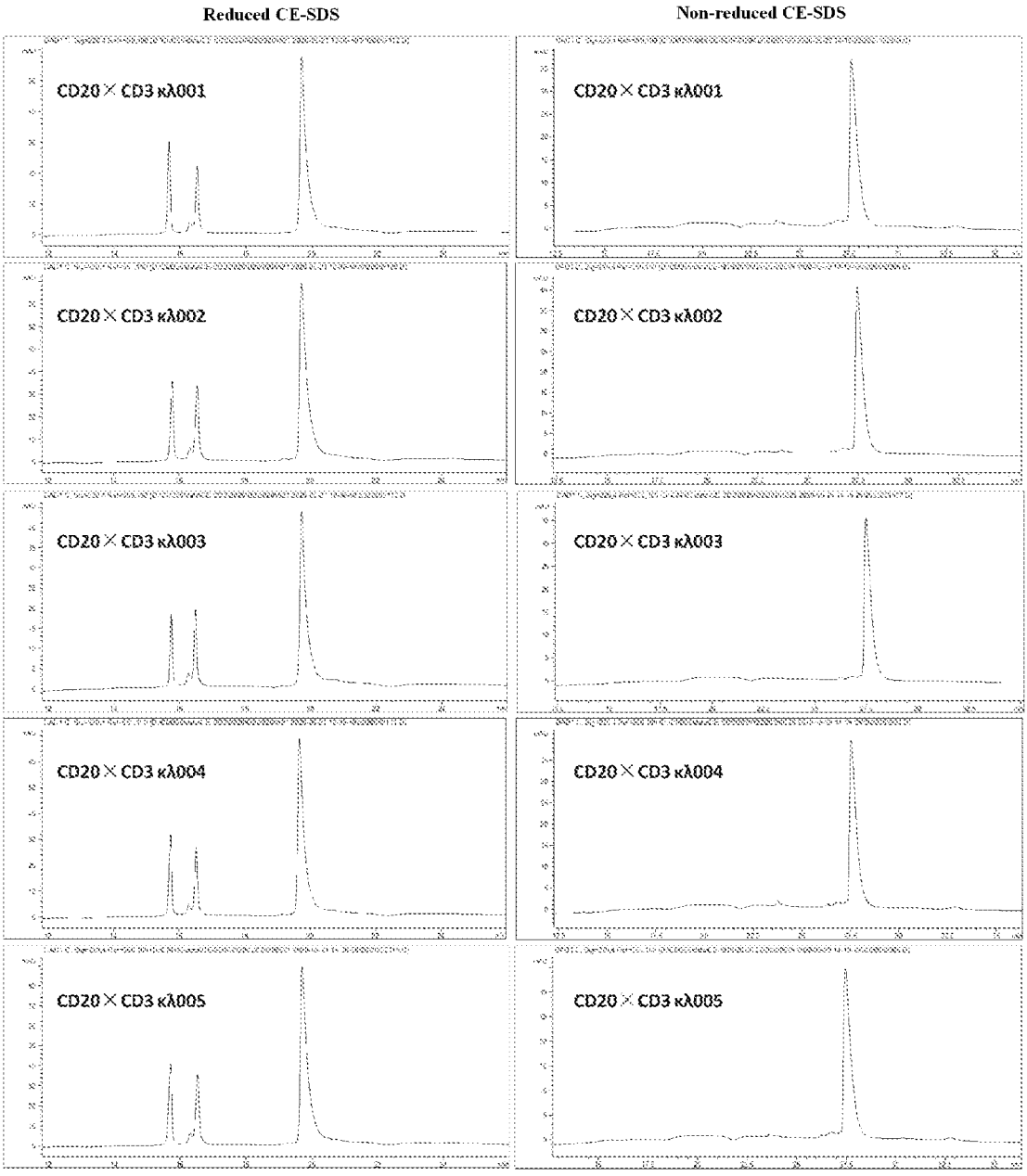

Reduced CE-SDS
Non-reduced CE-SDS
CD20×CD3 κλ001
CD20×CD3 κλ001
CD20×CD3 κλ002
CD20×CD3 κλ002
CD20×CD3 κλ003
CD20×CD3 κλ003
CD20×CD3 κλ004
CD20×CD3 κλ004
CD20×CD3 κλ005
CD20×CD3 κλ005

Figure 6

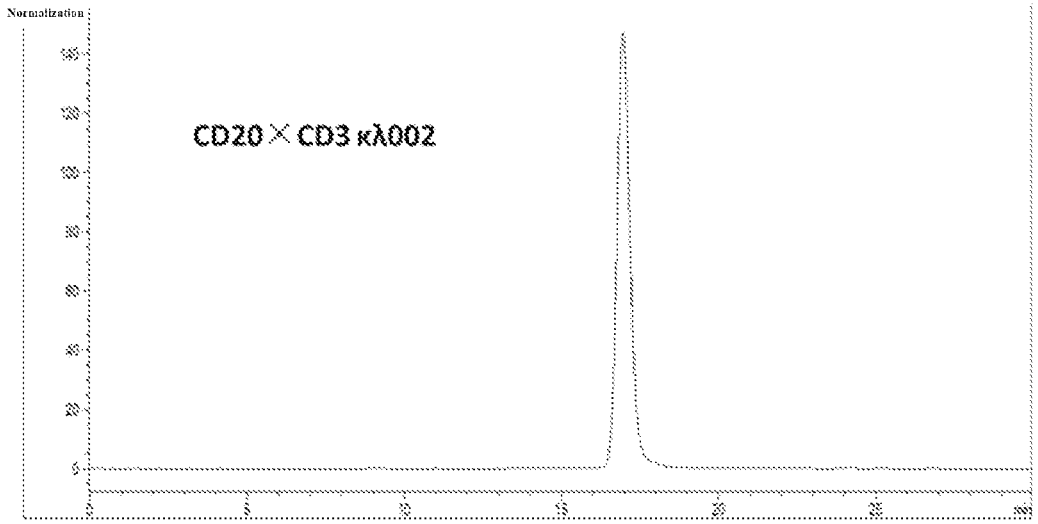


Figure 7

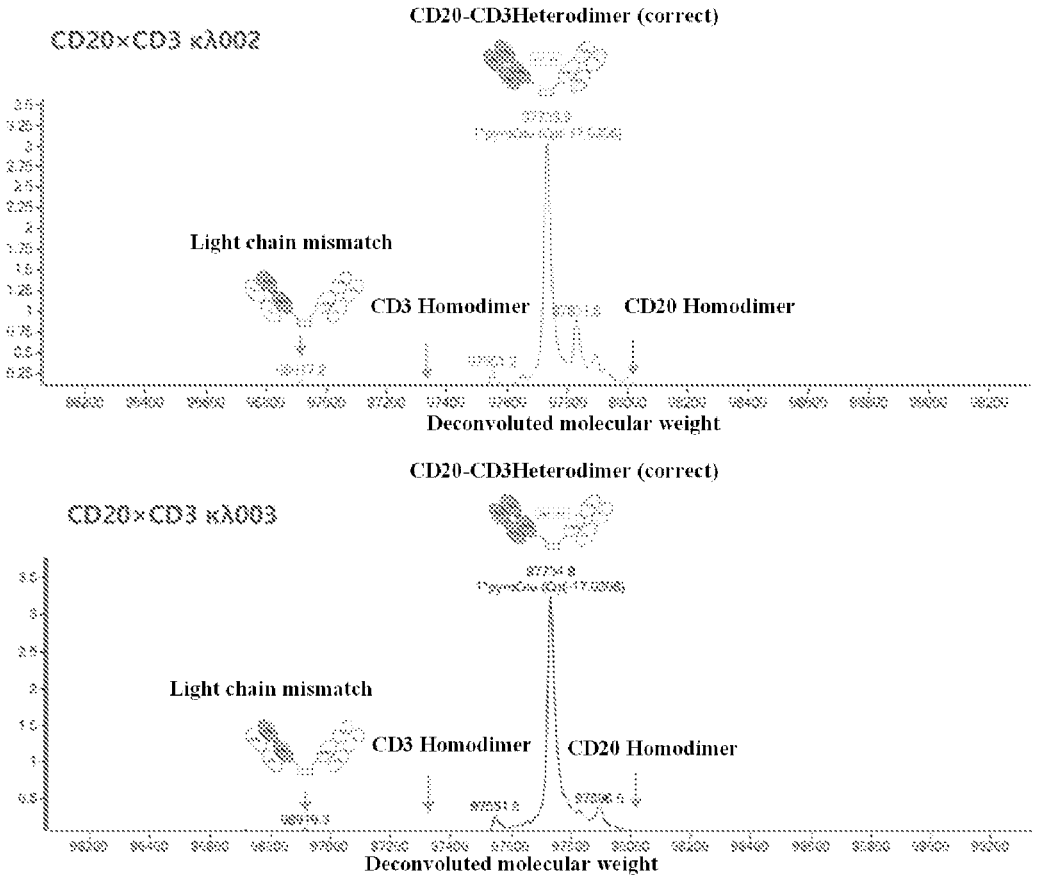


Figure 8

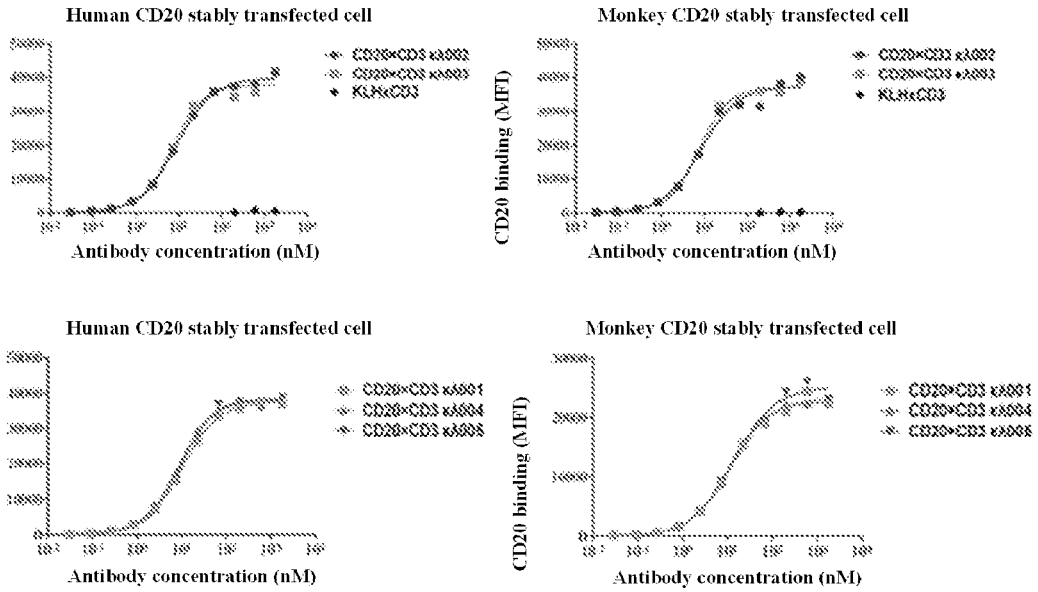

Human CD20 stably transfected cell
Monkey CD20 stably transfected cell
CD20 binding (MFI)
Antibody concentration (nM)
Human CD20 stably transfected cell
Monkey CD20 stably transfected cell
CD20 binding (MFI)
Antibody concentration (nM)

Figure 9

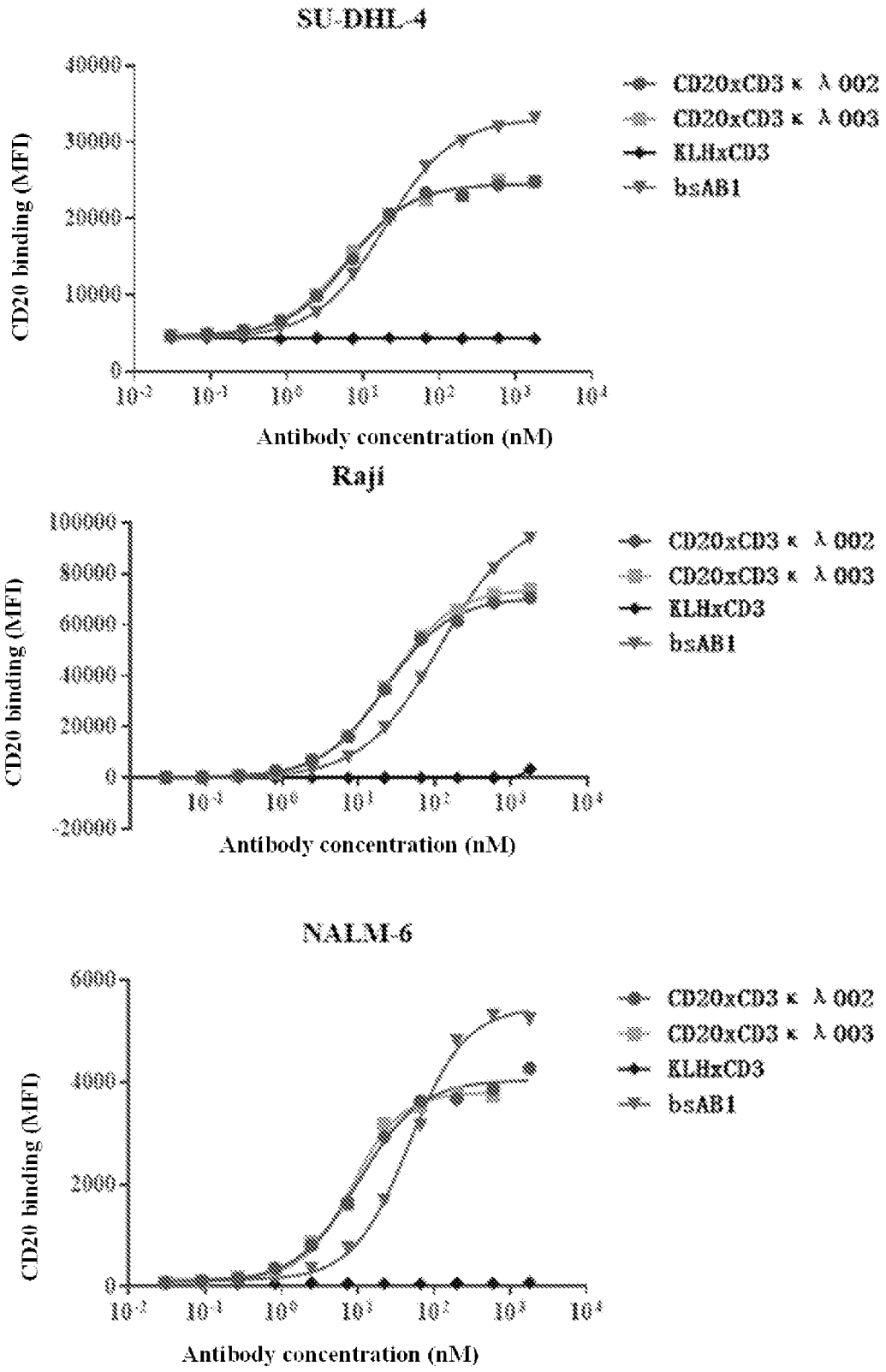

SU-DHL-4
CD20 binding (MFI)
40000
30000
20000
10000
0
10^{-2} 10^{-1} 10^{0} 10^{1} 10^{2} 10^{3} 10^{4}
Antibody concentration (nM)
CD20xCD3 κ λ 002
CD20xCD3 κ λ 003
KLHxCD3
bsAB1
Raji
CD20 binding (MFI)
100000
80000
60000
40000
20000
0
-20000
10^{-1} 10^{0} 10^{1} 10^{2} 10^{3} 10^{4}
Antibody concentration (nM)
CD20xCD3 κ λ 002
CD20xCD3 κ λ 003
KLHxCD3
bsAB1
NALM-6
CD20 binding (MFI)
6000
4000
2000
0
10^{-2} 10^{-1} 10^{0} 10^{1} 10^{2} 10^{3} 10^{4}
Antibody concentration (nM)
CD20xCD3 κ λ 002
CD20xCD3 κ λ 003
KLHxCD3
bsAB1

Figure 10

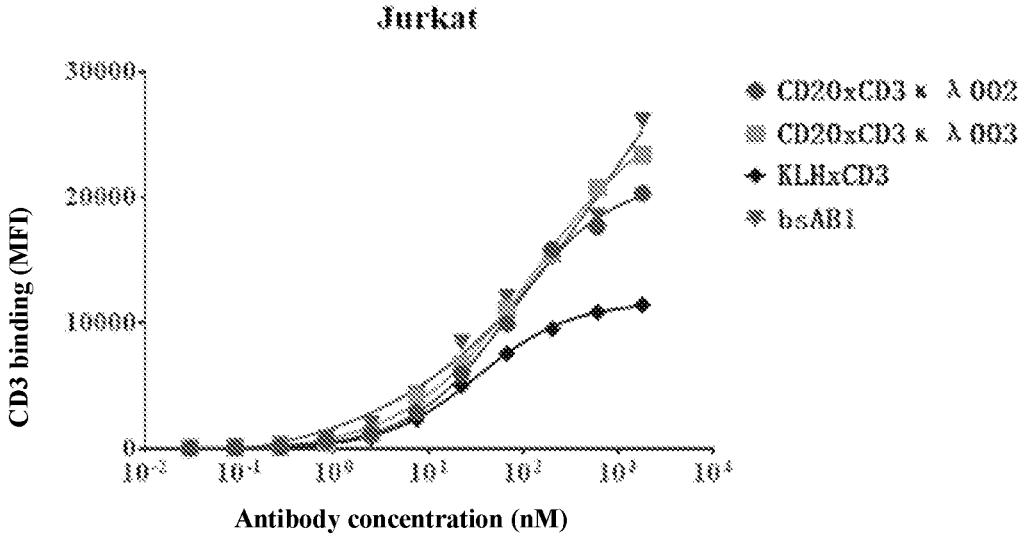


Figure 11

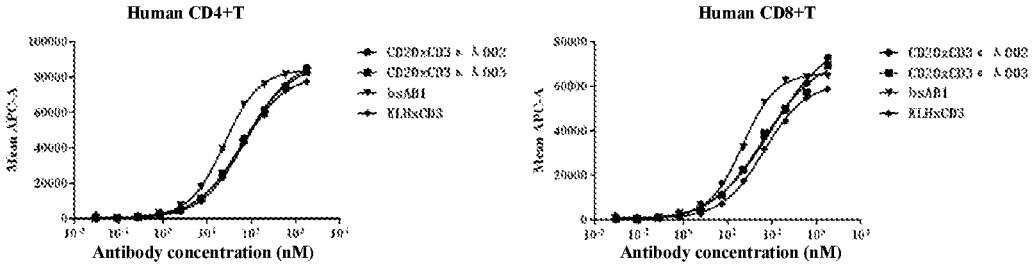


Figure 12

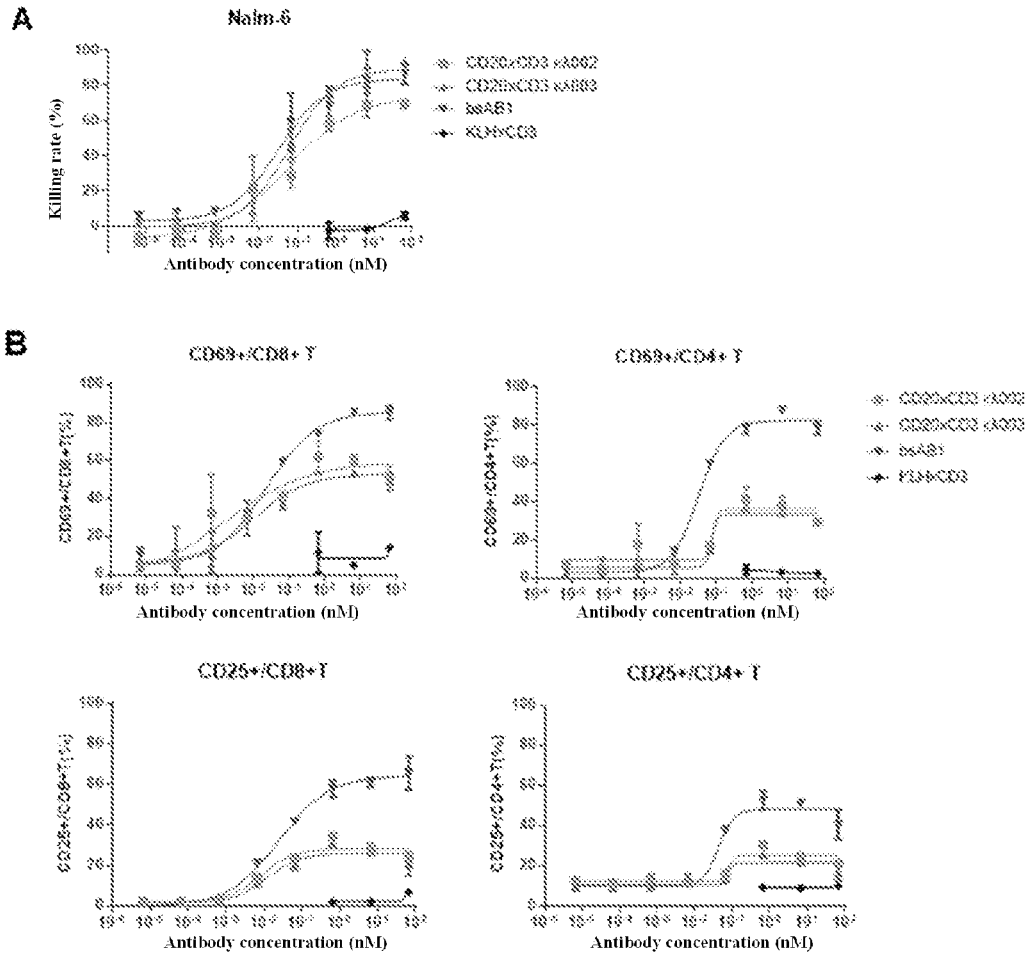

A
Nalm-6
Killing rate (%)
Antibody concentration (nM)
B
CD69+/CD8+ T
CD69+/CD4+ T
CD25+/CD8+ T
CD25+/CD4+ T
Antibody concentration (nM)

Figure 13

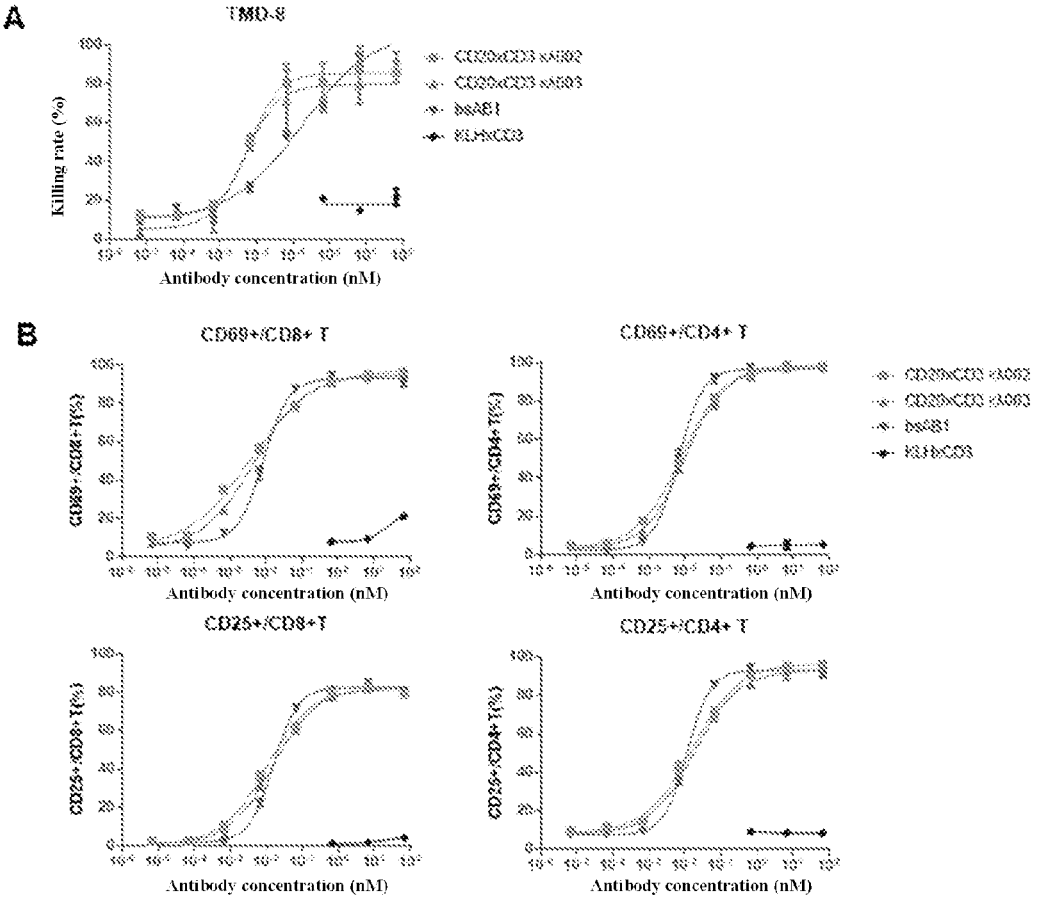

A
Killing rate (%)
Antibody concentration (nM)
B
CD69+/CD8+ T
CD69+/CD4+ T
CD25+/CD8+ T
CD25+/CD4+ T
Antibody concentration (nM)

Figure 14

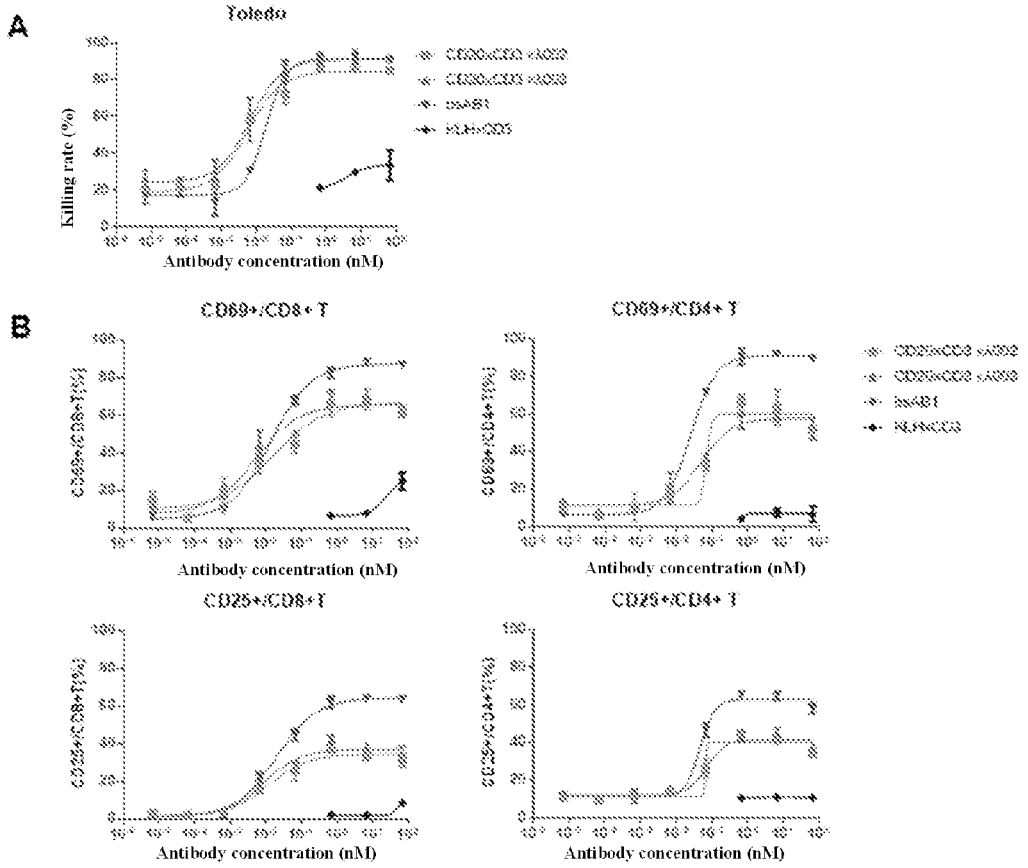


Figure 15

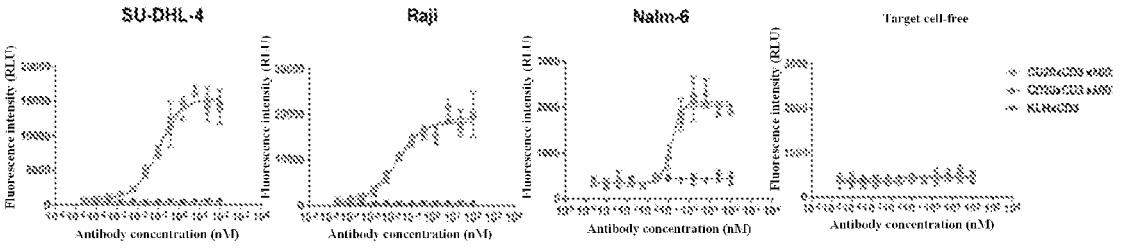


Figure 16

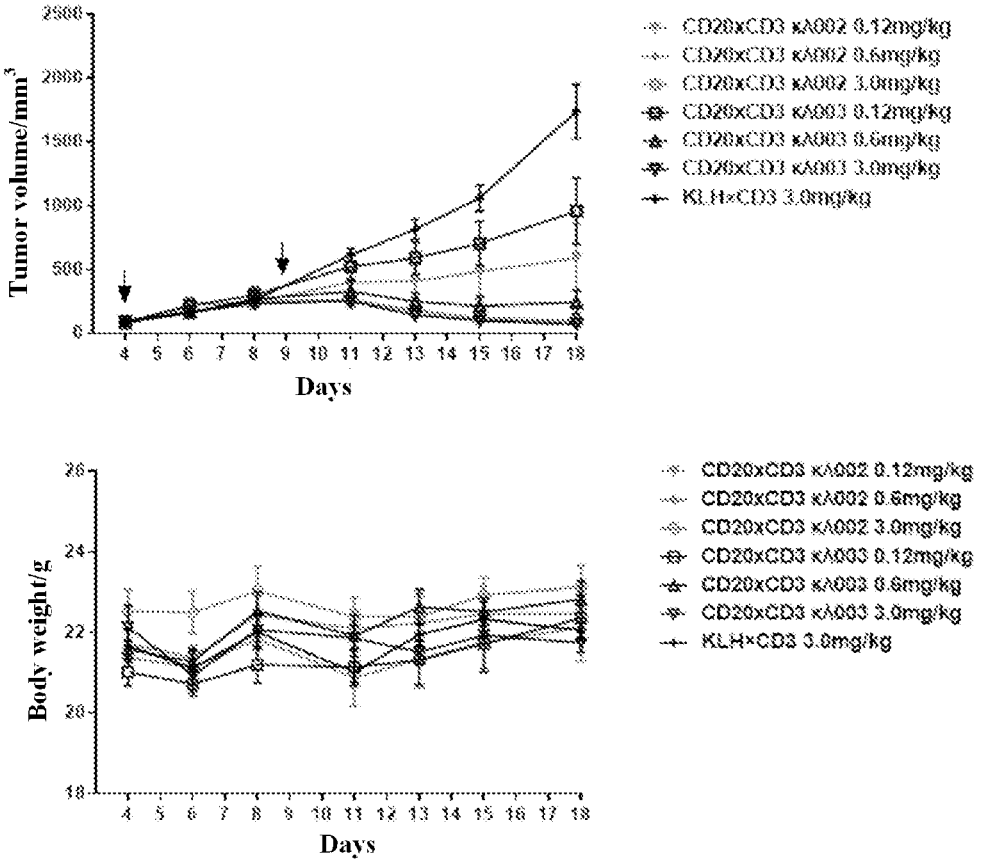

Tumor volume/mm3
2500
2000
1500
1000
500
0
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Days
CD20xCD3 κλ002 0.12mg/kg
CD20xCD3 κλ002 0.6mg/kg
CD20xCD3 κλ002 3.0mg/kg
CD20xCD3 κλ003 0.12mg/kg
CD20xCD3 κλ003 0.6mg/kg
CD20xCD3 κλ003 3.0mg/kg
KLHxCD3 3.0mg/kg
Body weight/g
26
24
22
20
18
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Days
CD20xCD3 κλ002 0.12mg/kg
CD20xCD3 κλ002 0.6mg/kg
CD20xCD3 κλ002 3.0mg/kg
CD20xCD3 κλ003 0.12mg/kg
CD20xCD3 κλ003 0.6mg/kg
CD20xCD3 κλ003 3.0mg/kg
KLHxCD3 3.0mg/kg

Figure 17

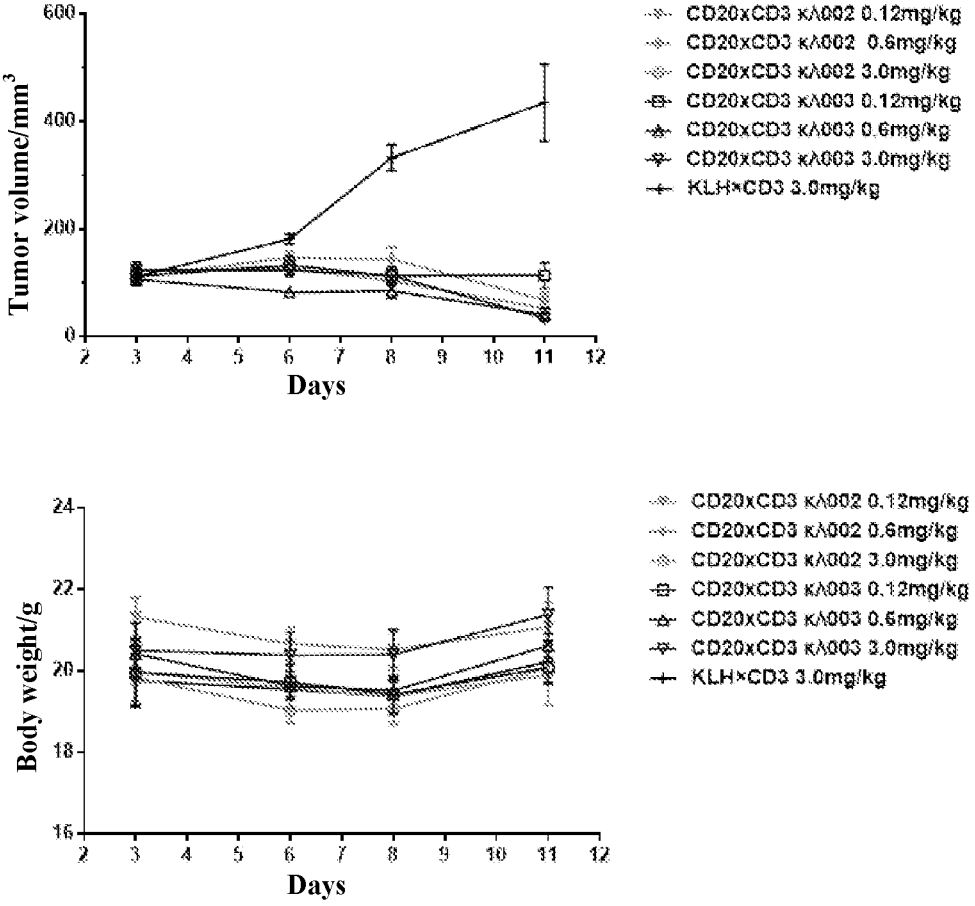


Figure 18

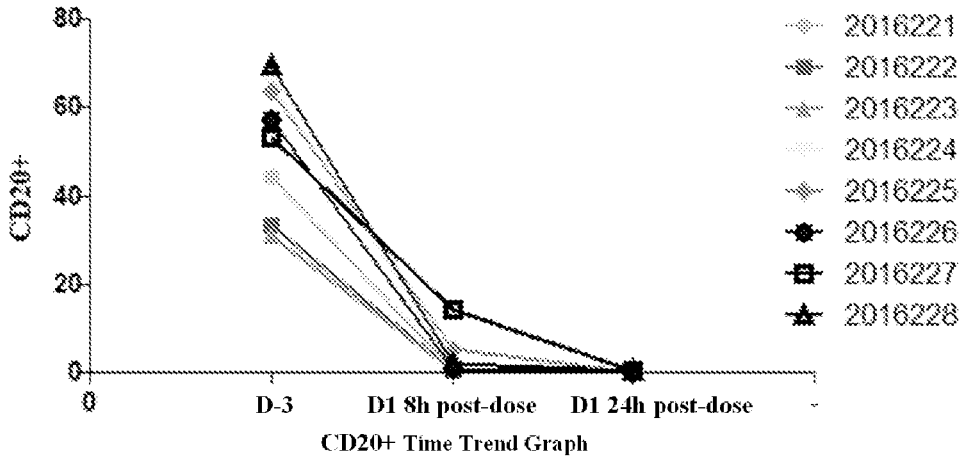


Figure 19

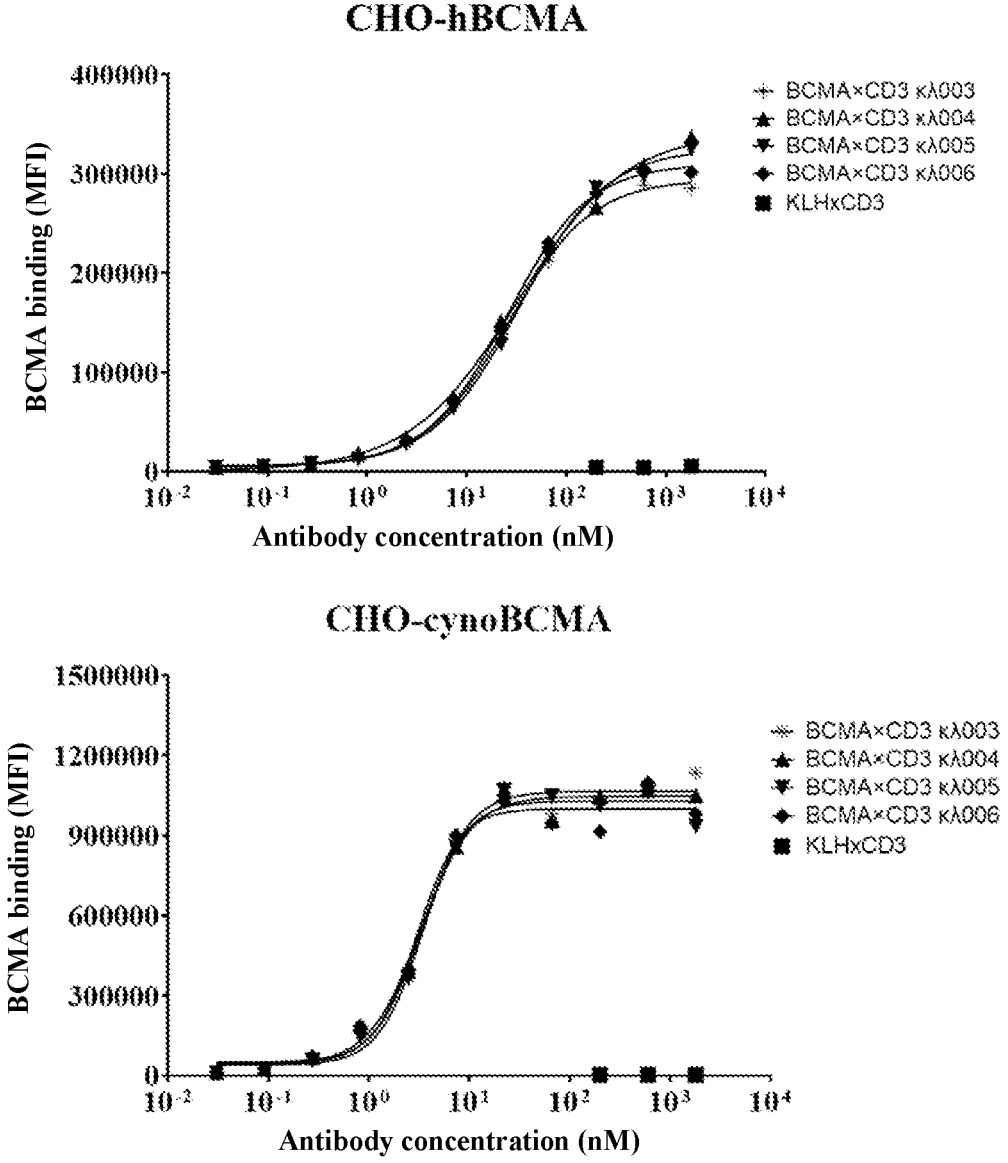

CHO-hBCMA
BCMA binding (MFI)
400000
300000
200000
100000
0
10-2
10-1
100
101
102
103
104
Antibody concentration (nM)
BCMA×CD3 κλ003
BCMA×CD3 κλ004
BCMA×CD3 κλ005
BCMA×CD3 κλ006
KLHxCD3
CHO-cynoBCMA
BCMA binding (MFI)
1500000
1200000
900000
600000
300000
0
10-2
10-1
100
101
102
103
104
Antibody concentration (nM)
BCMA×CD3 κλ003
BCMA×CD3 κλ004
BCMA×CD3 κλ005
BCMA×CD3 κλ006
KLHxCD3

Figure 20

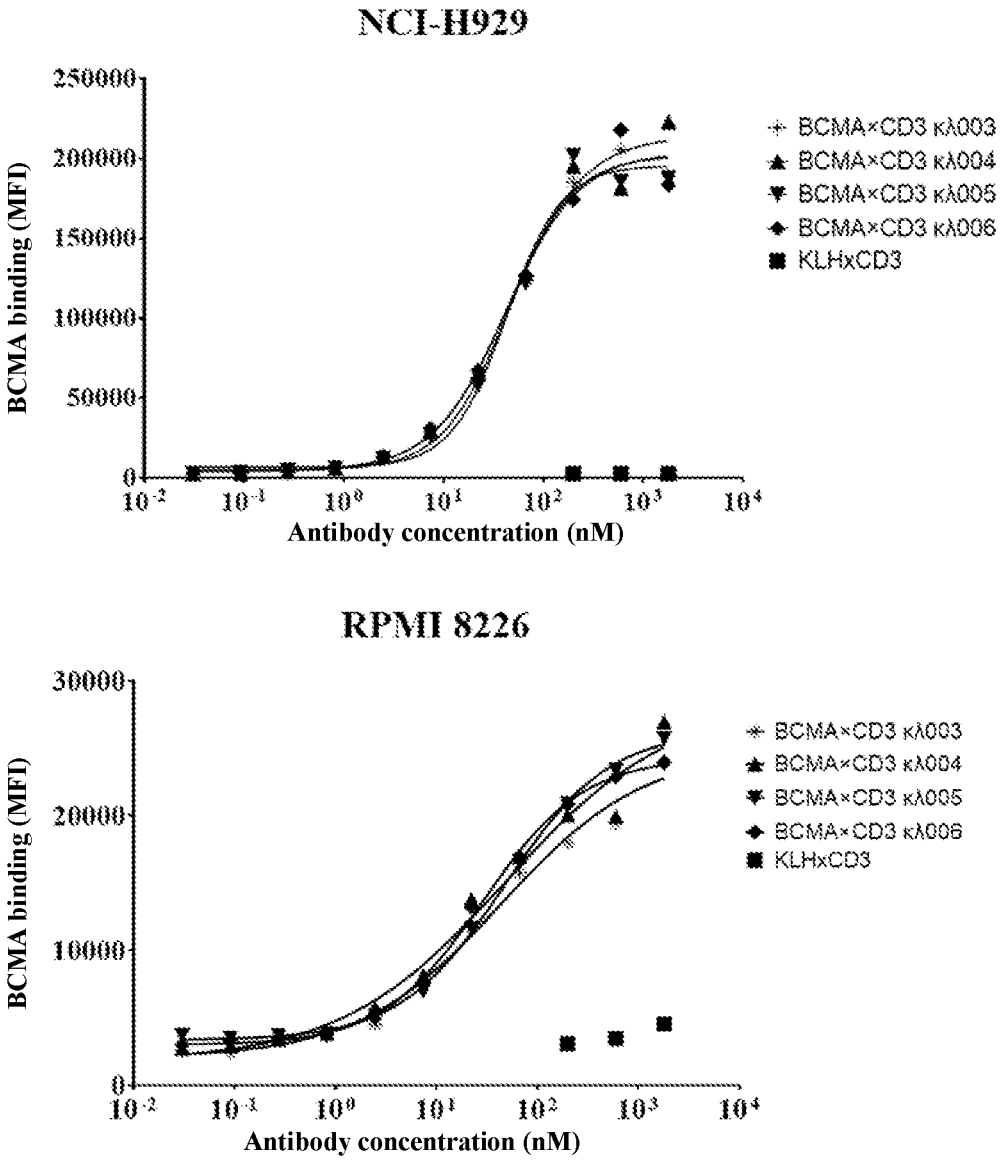

NCI-H929
BCMA binding (MFI)
250000
200000
150000
100000
50000
0
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
10^{4}
Antibody concentration (nM)
BCMA×CD3 κλ003
BCMA×CD3 κλ004
BCMA×CD3 κλ005
BCMA×CD3 κλ006
KLHxCD3
RPMI 8226
BCMA binding (MFI)
30000
20000
10000
0
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
10^{4}
Antibody concentration (nM)
BCMA×CD3 κλ003
BCMA×CD3 κλ004
BCMA×CD3 κλ005
BCMA×CD3 κλ006
KLHxCD3

Figure 21

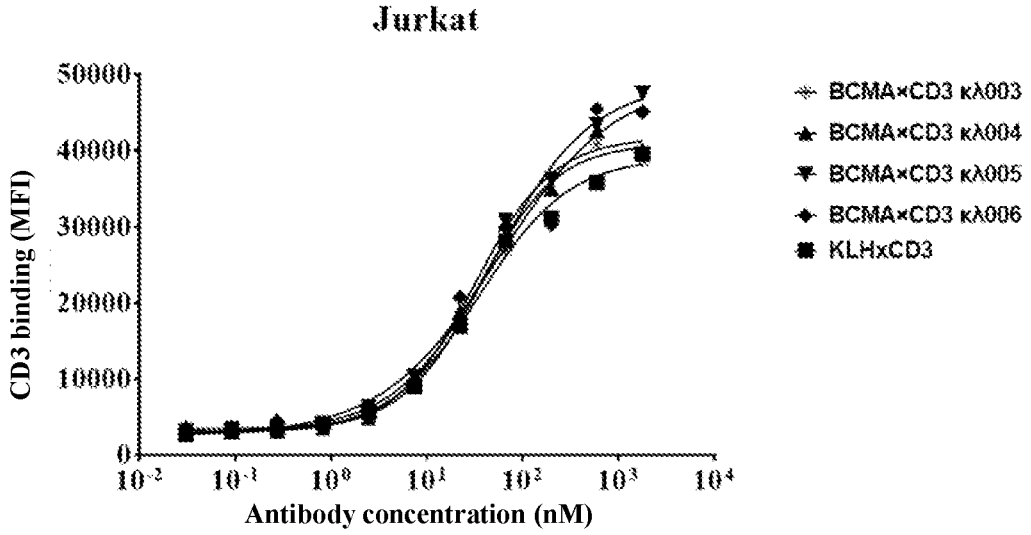


Figure 22

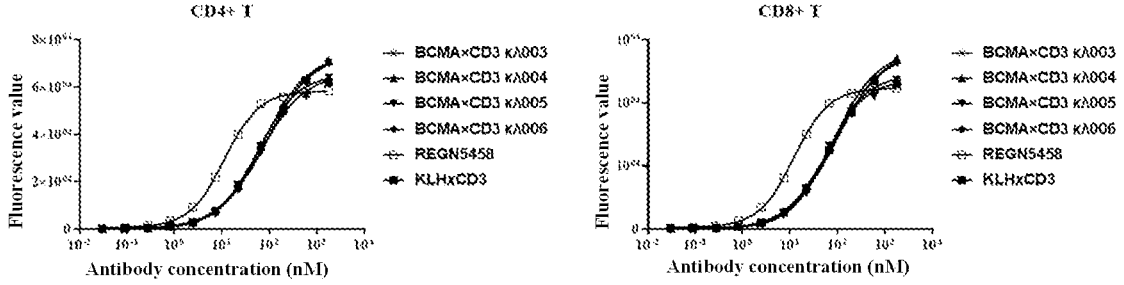


Figure 23

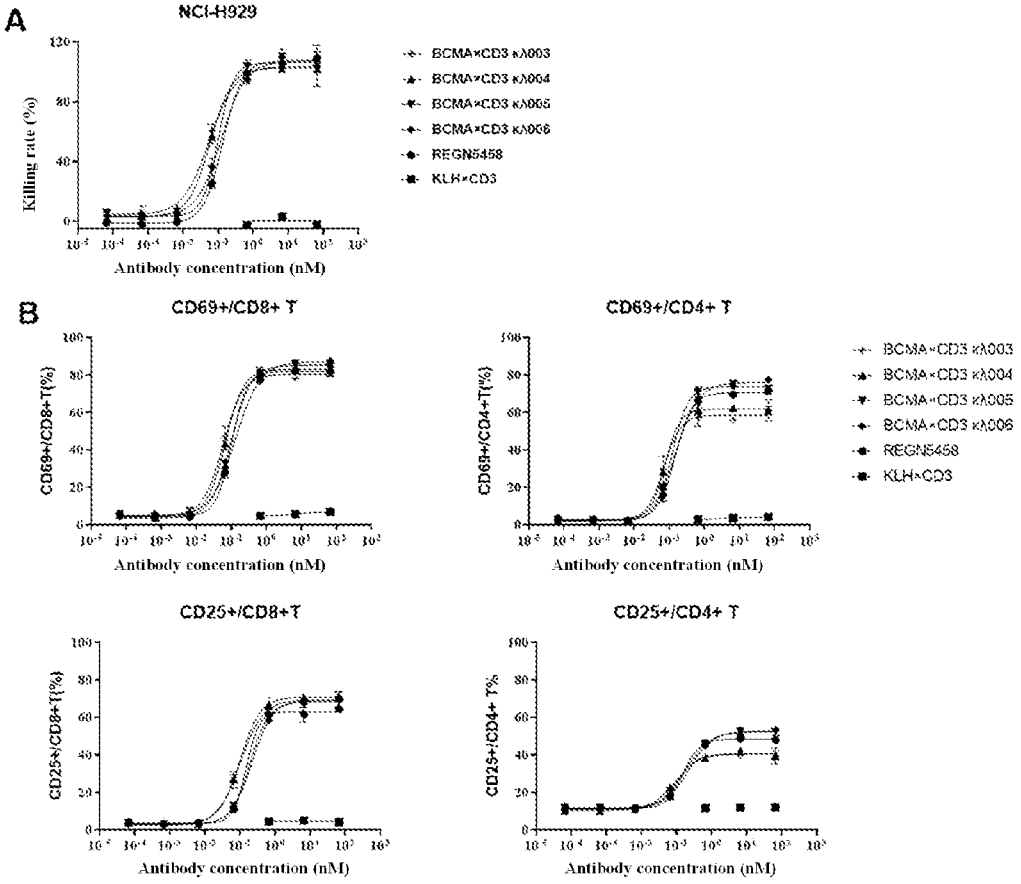

A
NCI-H929
Killing rate (%)
Antibody concentration (nM)
BCMA×CD3 κλ003
BCMA×CD3 κλ004
BCMA×CD3 κλ005
BCMA×CD3 κλ006
REGN5458
KLH×CD3
B
CD69+/CD8+ T
CD69+/CD8+T(%)
CD69+/CD4+ T
CD69+/CD4+T(%)
CD25+/CD8+T
CD25+/CD8+T(%)
CD25+/CD4+ T
CD25+/CD4+ T%

Figure 24

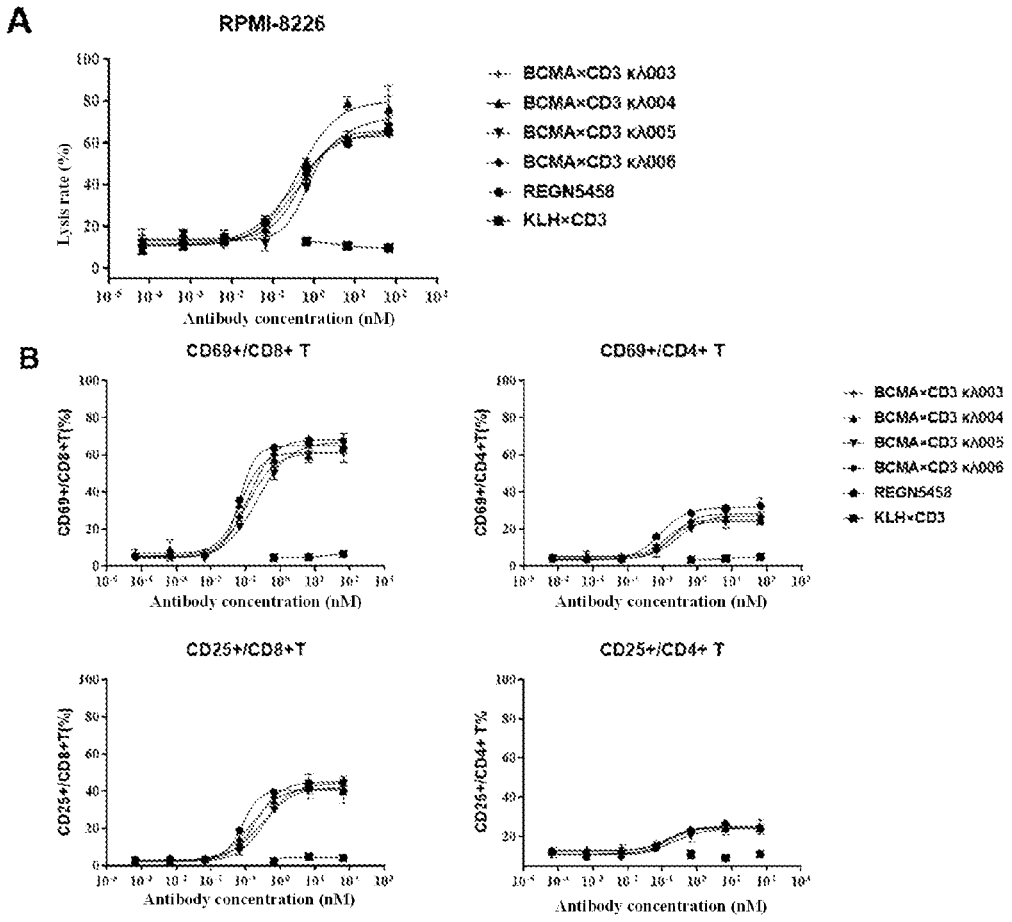


Figure 25

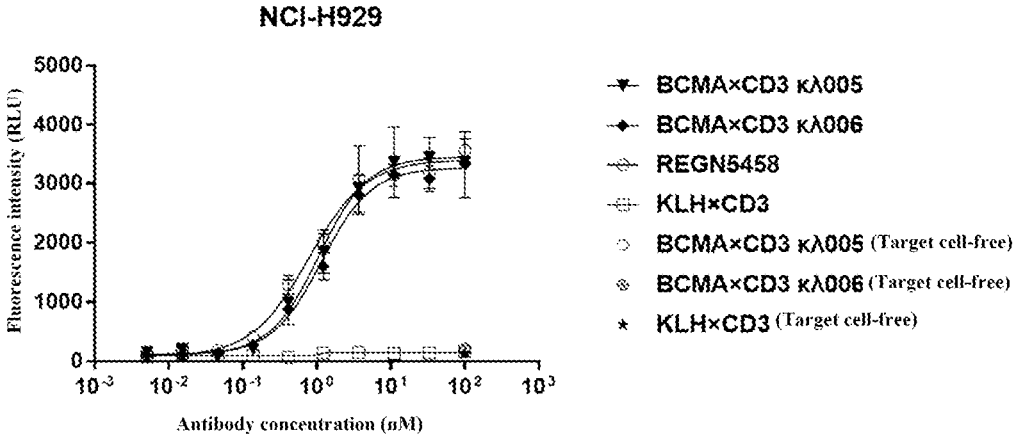


Figure 26

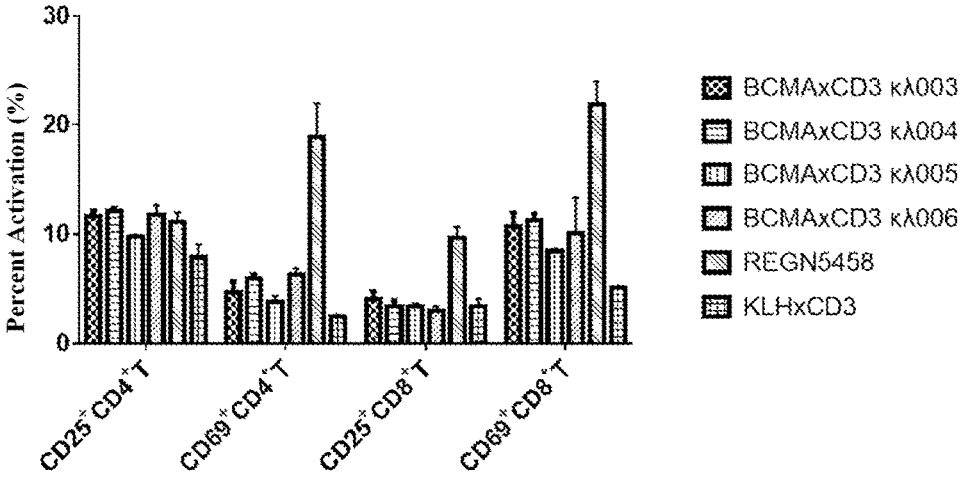


Figure 27

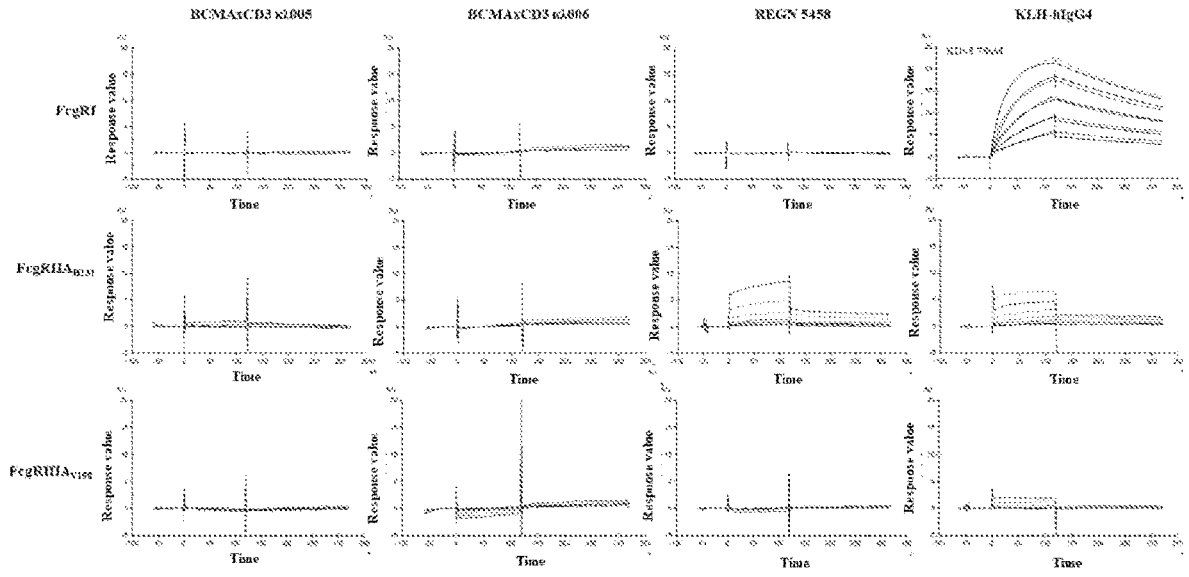


Figure 28

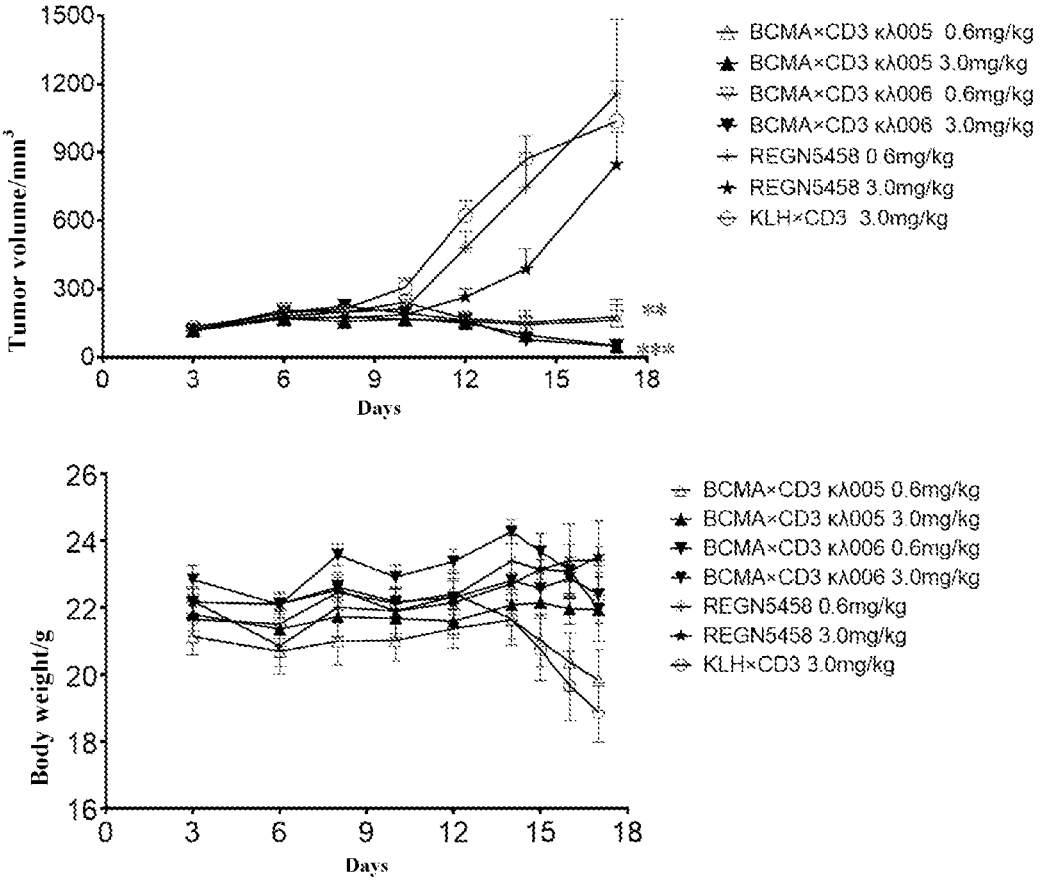

Tumor volume/mm3
1500
1200
900
600
300
0
0
3
6
9
12
15
18
Days
**
***
BCMA×CD3 κλ005 0.6mg/kg
BCMA×CD3 κλ005 3.0mg/kg
BCMA×CD3 κλ006 0.6mg/kg
BCMA×CD3 κλ006 3.0mg/kg
REGN5458 0.6mg/kg
REGN5458 3.0mg/kg
KLH×CD3 3.0mg/kg
Body weight/g
26
24
22
20
18
16
0
3
6
9
12
15
18
Days
BCMA×CD3 κλ005 0.6mg/kg
BCMA×CD3 κλ005 3.0mg/kg
BCMA×CD3 κλ006 0.6mg/kg
BCMA×CD3 κλ006 3.0mg/kg
REGN5458 0.6mg/kg
REGN5458 3.0mg/kg
KLH×CD3 3.0mg/kg

Figure 29

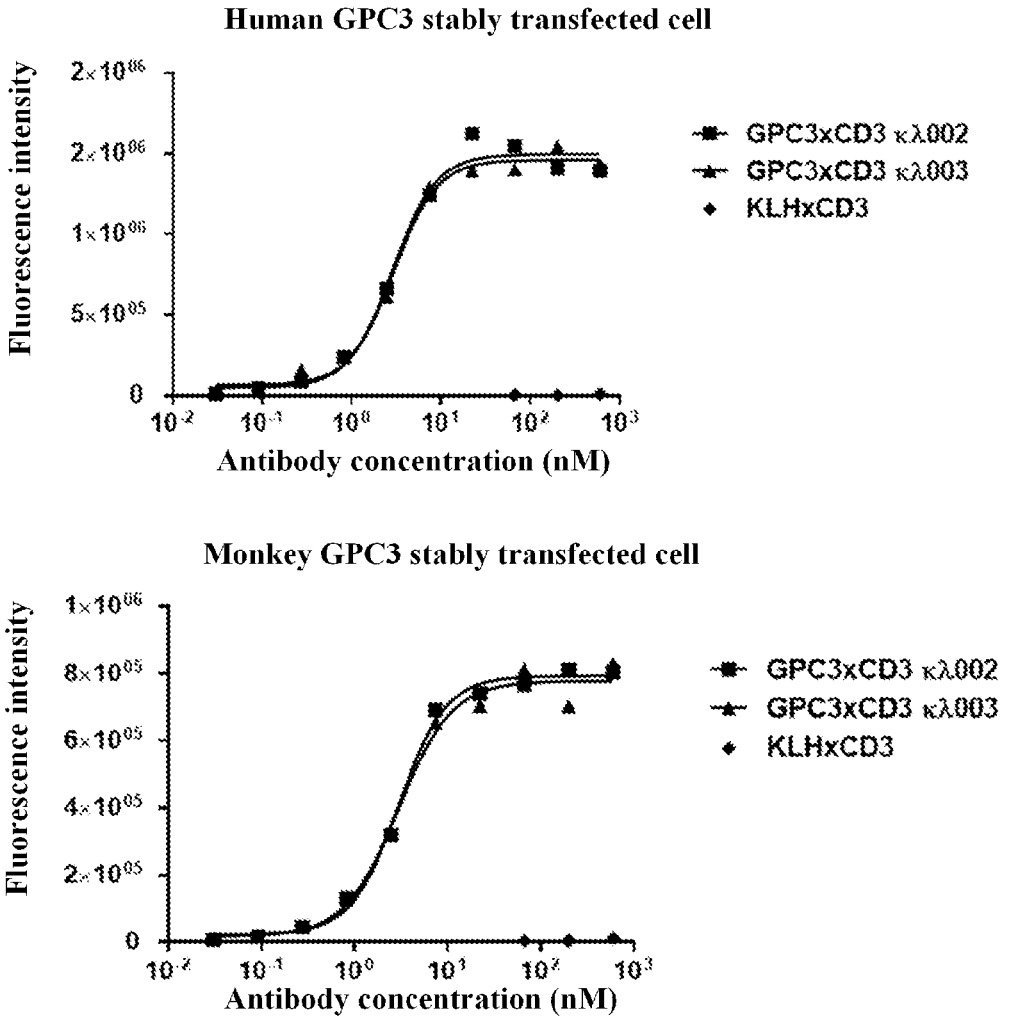


Figure 30

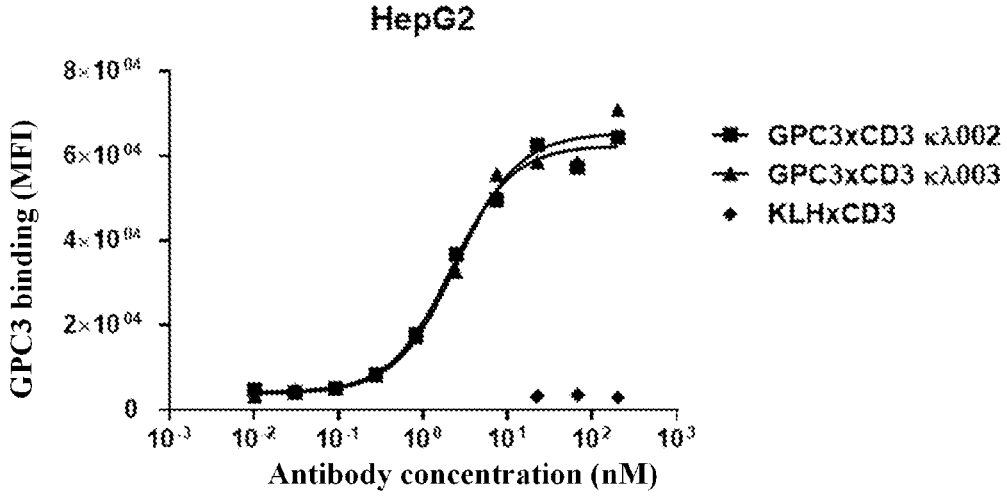


Figure 31

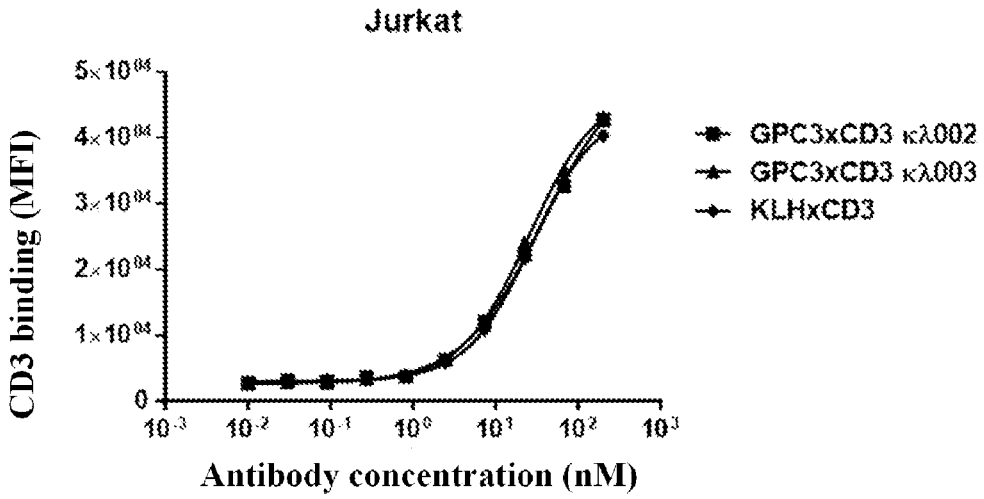


Figure 32

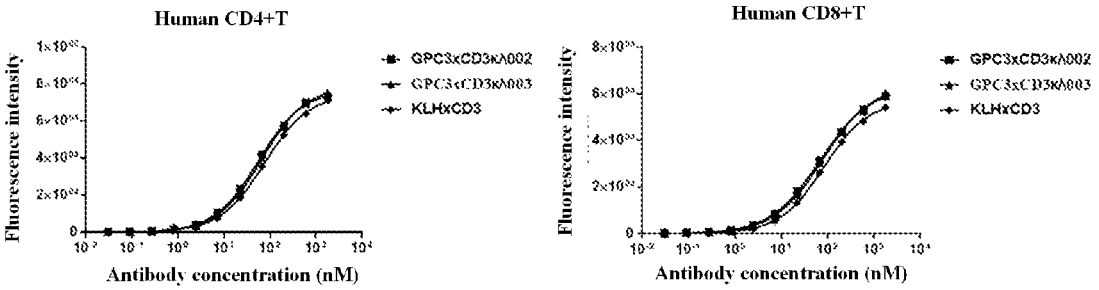


Figure 33

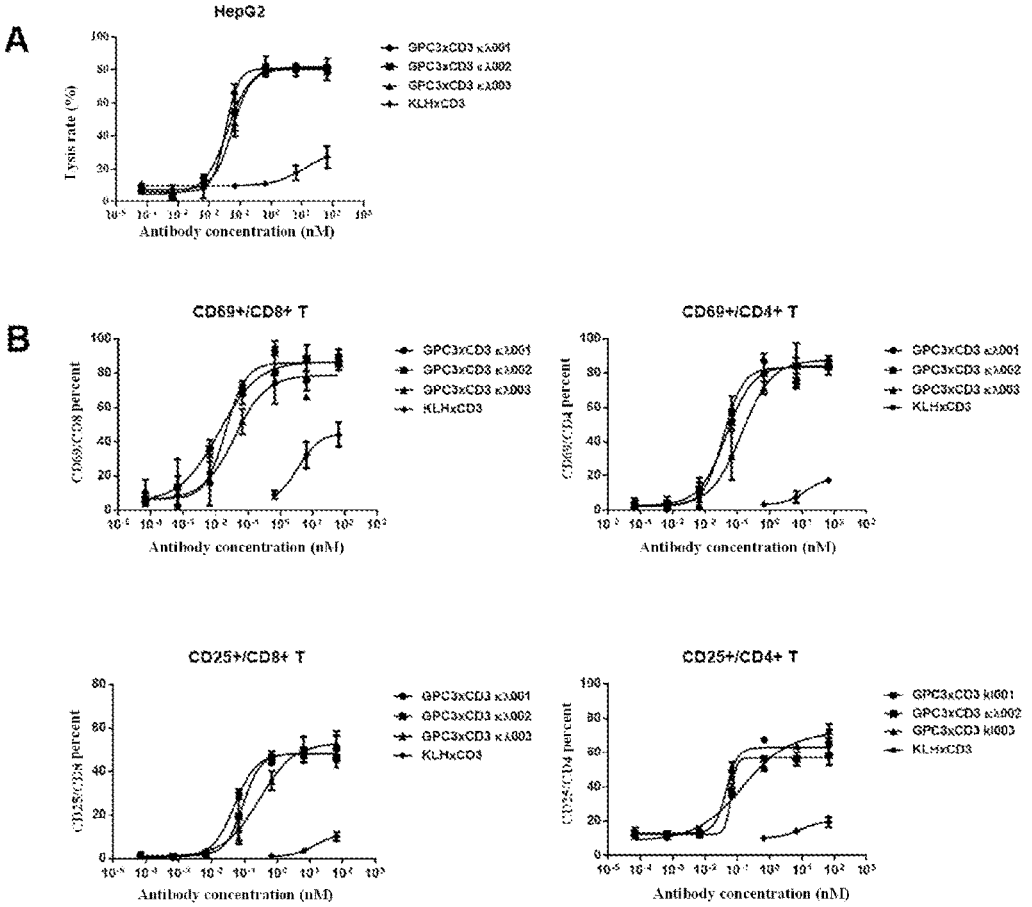


Figure 34

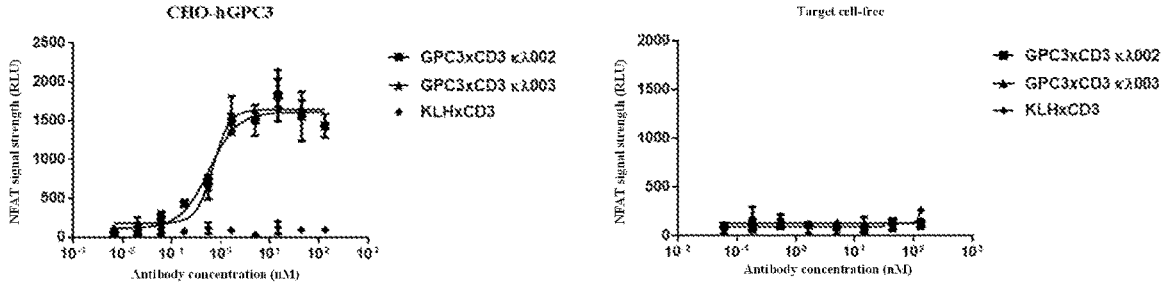


Figure 35

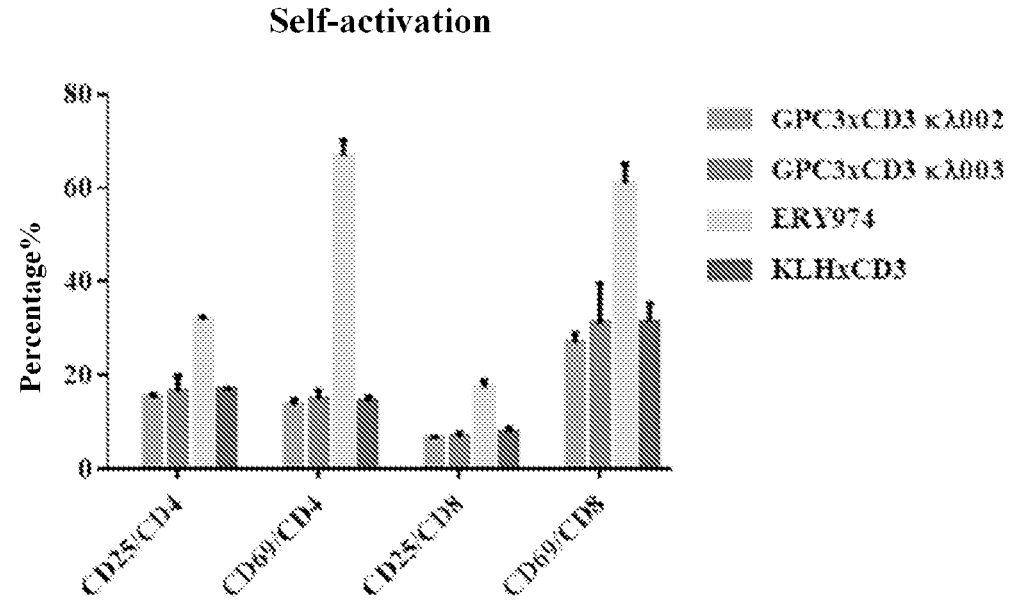


Figure 36

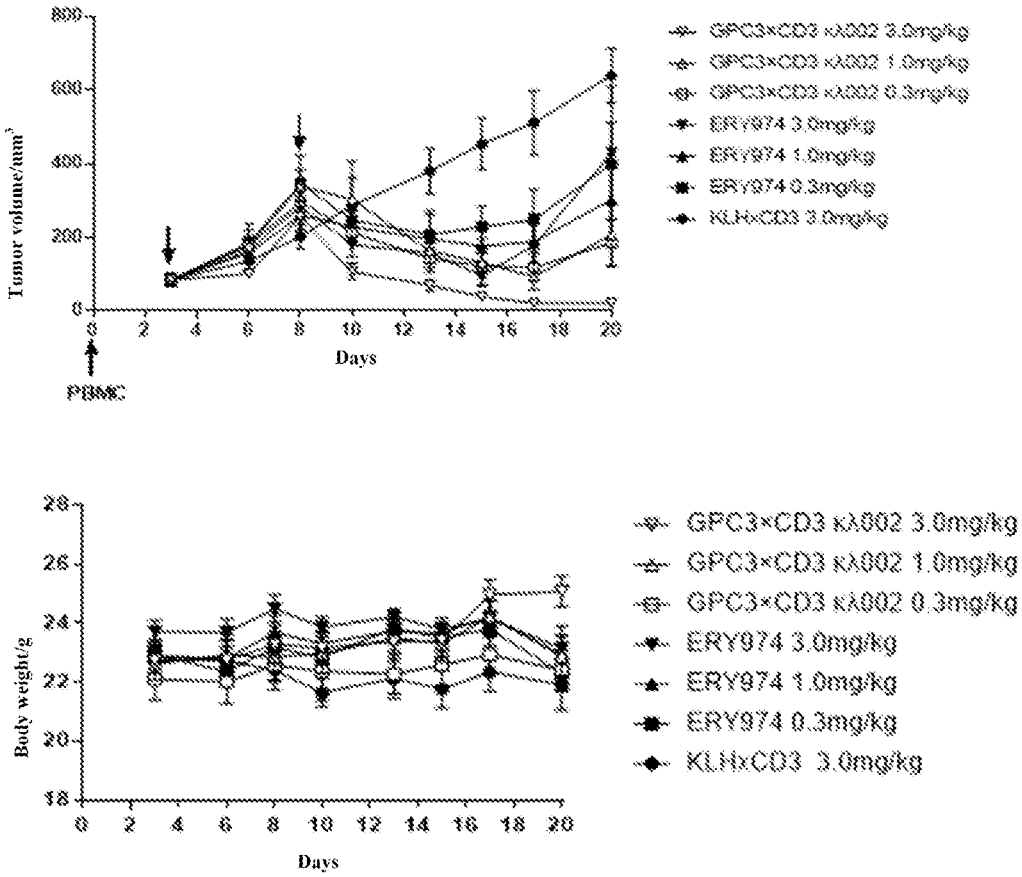


Figure 37

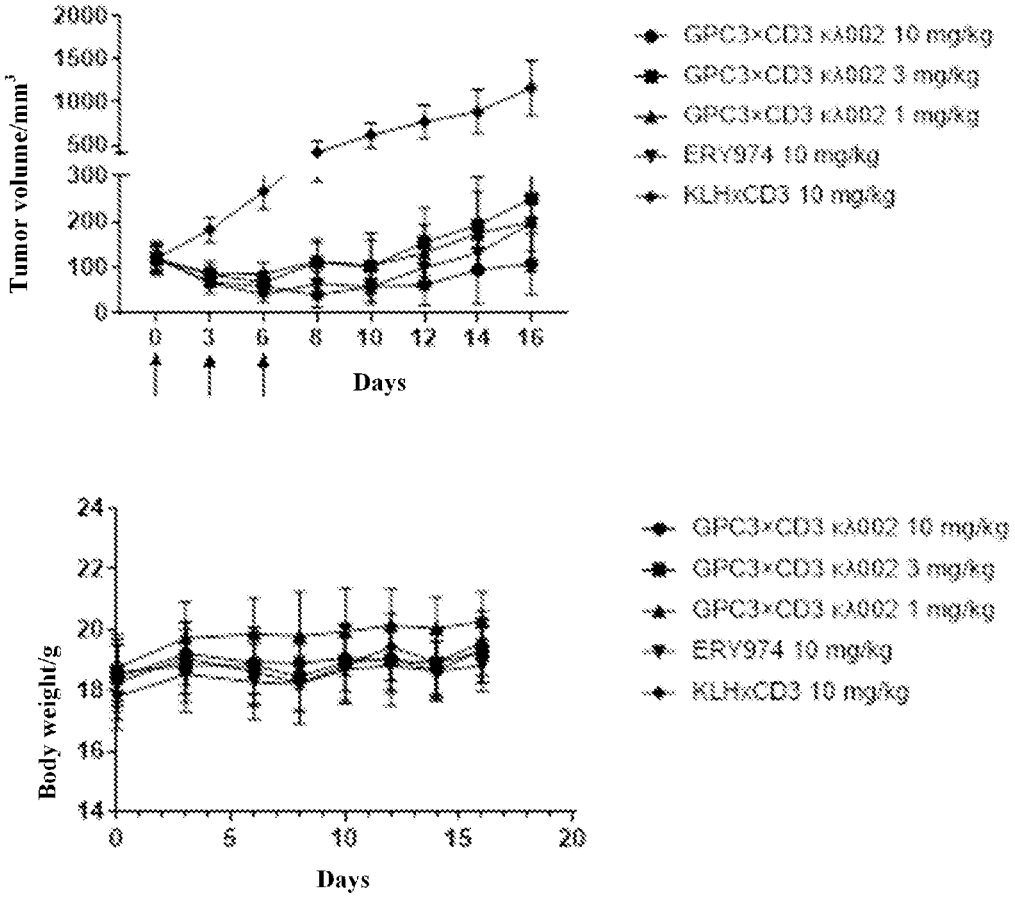

Tumor volume/mm3
2000
1500
1000
500
300
200
100
0
0 3 6 8 10 12 14 16
Days
GPC3×CD3 κλ002 10 mg/kg
GPC3×CD3 κλ002 3 mg/kg
GPC3×CD3 κλ002 1 mg/kg
ERY974 10 mg/kg
KLH×CD3 10 mg/kg
Body weight/g
24
22
20
18
16
14
0 5 10 15 20
Days
GPC3×CD3 κλ002 10 mg/kg
GPC3×CD3 κλ002 3 mg/kg
GPC3×CD3 κλ002 1 mg/kg
ERY974 10 mg/kg
KLH×CD3 10 mg/kg

Figure 38

BISPECIFIC ANTIBODY AND USE THEREOF

TECHNICAL FIELD

[0001] The present disclosure relates to a bispecific antibody and use thereof, particularly a bispecific antibody that binds CD3 and another antigen, and use thereof.

BACKGROUND ART

[0002] A T-cell bispecific antibody (or T-cell adaptor) is a specific antibody molecule, through which recognizes a target cell surface antigen (antigen arm) at one end and binds to a T-cell CD3 receptor (CD3 arm) at the other end, CD3 on T-cells may be aggregated in a manner similar to TCR/peptide/HLA, thereby activating T-cells and killing tumors. In the 1980s, it was reported that tumor cells were killed by using bispecific antibodies (Staerz U D., Nature. 1985 Apr. 18-24; 314(6012):628-31; Perez P. et al. Nature. 1985 Jul. 25-31; 316(6026):354-6). After more than 30 years of research, the problem of antibody mismatch has been substantially solved, and three bispecific antibody drugs have been successively approved for marketing. Although these bispecific antibodies show very good therapeutic effects in approved indications, the concomitant side effects and limitations in use preclude widespread applications of these bispecific antibodies in the early days. For example: early-marketed catumaxomab has been withdrawn from the market, because the Fc fragment binds to Fcγ receptor expressed by liver Kupffer cells, which triggers a rapid cytokine release. Regarding the blinatumomab launched in 2014, due to the use of Fv antibody fragments, the biological half-life is only 2 hours, it requires a low-dose continuous intravenous infusion, and is approved by FDA together with a black-box warning on cytokine release syndrome and neurological toxicities.

[0003] During a normal immune response, TCR is binded with low affinity (about 1-100 μM) to foreign peptide-human leukocyte antigen complexes (HLA) on infected or mutated cells, an activation signal is transduced into the nucleus via CD3 signaling complexes (including CD3εγ, CD3εδ and CD3ζζ), activating the expression of transcription factors and their downstream proteins (cytokines, granzymes, perform, etc.), wherein the signal intensity generated by the TCR complexes will determine the fate of T-cells. The early developed CD3 bispecific antibodies, mostly based on a small number of murine antibodies such as OKT3, L2K, UCHT1, TR66 and the like, have high affinity, leading to excessive activation of T-cells and release of a large number of cytokines and resulting in cytokine storm syndrome. At the same time, the high affinity also leads to the enrichment of bispecific antibodies in secondary lymphoid organs, and reduces the exposure to tumor tissue.

[0004] The binding ability of Fc portion of the antibody to Fcγ receptor is another important factor affecting drug safety. Since Fcγ receptor is expressed in various normal tissues, after the bi-specific antibody binds to Fcγ receptor on cell membrane through Fc, it can result in cross-linking activation of CD3 receptor bound at the other end due to Fcγ receptor aggregation, thereby resulting in severe off-target toxicity. By using a human IgG2 subtype or IgG4 subtype which has a weak Fcγ receptor binding ability, or further performing amino acid substitutions at the corresponding positions in CH2, for example: positions 233-236 (EU sequence numbering) of IgG1 and IgG4 are substituted with the corresponding sequence of IgG2 by Armour etc. so as to reduce the binding to Fcγ receptors (Armour K L, et al, Recombinant human IgG molecules lacking Fcgamma receptor I binding and monocyte triggering activities, Eur J Immunol. 1999 August; 29(8):2613-24). Newman etc. introduced mutations Ser228Pro and Leu235Glu in IgG4, stabilizing the IgG4 structure while reducing binding to Fcγ receptors (Newman R, et al, Modification of the Fc region of a primatized IgG antibody to human CD4 retains its ability to modulate CD4 receptors but does not deplete CD4(+) T-cells in chimpanzees. Clin Immunol. 2001 February; 98(2):164-74). Idusogie etc. found that respectively substituting Asp270, Lys322, Pro329 or Pro331 with Ala could reduce the binding of IgG1 to complement C1q (Idusogie E E, et al, Mapping of the C1q binding site on rituxan, a chimeric antibody with a human IgG1 Fc. J Immunol. 2000 Apr. 15; 164(8):4178-84), etc.

[0005] Interstrand mismatches are major process difficulties in the development of natural IgG-like bispecific antibodies. A common light chain invented by Merchant A M etc. (Merchant A M, et al, An efficient route to human bispecific IgG. Nat Biotechnol. 1998. PMID: 9661204) or a common heavy chain developed by Fischer N etc. (Fischer N, et al, Exploiting light chains for the scalable generation and platform purification of native human bispecific IgG. Nat Commun. 2015 Feb. 12; 6:6113) often require complicated protein engineering-modifications or be produced from transgenic animals (McWhirter J, et al, Common light chain mouse. WO2011097603. 2011); Carter Pet al. (Atwell S, et al, Stable heterodimers from remodeling the domain interface of a homodimer using a phage display library, J Mol Biol. 1997 Jul. 4; 270(1):26-35), resolving mismatches between heavy chains by introducing a knobs-into-holes complementary mutation in the Fc portion of the antibody. Schaefer G etc. (Schaefer W, et al, Immunoglobulin domain crossover as a generic approach for the production of bispecific IgG antibodies, Proc Natl Acad Sci USA. 2011) developed the CrossMab technique that exchanges the Fab part or full length of the light and heavy chains to solve the mismatch problem of a light chain, wherein the partially exchanged CrossMab$^{VH\text{-}VL}$ and CrossMab$^{CH1\text{-}CL}$ require the introduction of additional peptide segments to achieve correct pairing, while the CrossMab^{Fab} with full length exchange has a correct pairing rate of less than 50%.

SUMMARY OF THE INVENTION

[0006] In expressing bispecific antibodies, the inventor has unexpectedly discovered that, by combining a humanized anti-CD3 antibody having a λ light chain with a targeting antibody having a κ light chain, the λ light chain of the anti-CD3 antibody is more likely to pair with a heavy chain of a homologous CD3, while the kappa light chain of the targeting antibody is more likely to pair with a heavy chain of a homologous targeting antibody. By further designing complementary charge pairs between the light and heavy chains, the efficiency of correct pairing can be improved. Furthermore, experimental examples prove that, the novel T-cell connector constructed by using antibodies having multiple targets such as CD20, BCMA and GPC3, and humanized anti-CD3 antibody may achieve a monomer purity of 98-100% and a very low mismatch ratio (<1%) after three-step purification.

[0007] The present disclosure provides a novel T-cell linker designed by using bispecific antibodies with different

types of light chains κλ, and a full-length IgG configuration, wherein in combination with the anti-CD3 antibody arms of target cells and T-cells, kappa light chain and lambda light chain are used to pair with their homologous heavy chains, and complementary charge pairs are introduced to enhance the correct pairing rate. By affinity optimization, activated T-cells can be recruited at low concentrations of the novel T-cell connector, resulting in effective killing of target cells, while T-cells are not be activated in the absence of target cells. At the same time, κ λ bispecific antibodies of the novel T-cell do not bind to FcγR receptors, reducing the risk of cytokine storm. The novel anti-CD20×CD3 κλ, bispecific antibody, anti-BCMA×CD3 κλ bispecific antibody, and anti-GPC3×CD3κλ bispecific antibody constructed using the methods of the present disclosure have high purification yields, which can obtain a purity of >99% purity by three-step purification. Animals have a good tolerance to the novel CD20-CD3 κλ bispecific antibody. The efficacy and safety of the novel T-cell connector are superior to similar antibodies.

[0008] In one aspect, the present disclosure provides a bispecific antibody or antigen-binding portion thereof.

[0009] In another aspect, the present disclosure provides nucleic acids encoding a bispecific antibody or antigen-binding portion thereof according to the previous aspect.

[0010] In another aspect, the present disclosure provides a vector comprising a nucleic acid of the previous aspect.

[0011] In another aspect, the present disclosure provides a cell comprising the vector of the previous aspect.

[0012] In the antibody or antigen-binding portion thereof according to any one of the preceding aspects, the antibody or antigen-binding portion thereof is humanized.

[0013] In another aspect, the present disclosure provides a pharmaceutical composition or the kit comprising the antibody or antigen-binding portion thereof, or nucleic acid encoding the same according to any of the preceding aspects, and a pharmaceutically acceptable carrier.

[0014] In another aspect, the present disclosure provides an antibody-drug conjugate, comprising the antibody or antigen-binding portion thereof, bispecific or multispecific molecule of any of the foregoing aspects which are covalently attached to a therapeutic moiety.

[0015] In another aspect, the present disclosure provides a method of treating a disease associated therewith, comprising the steps of: administering to the mammal a therapeutically effective amount of the antibody or antigen-binding fragment thereof, the nucleic acid, the vector, the cell and/or the pharmaceutical composition according to any of the preceding aspects.

[0016] In another aspect, the present disclosure provides a use of the antibody or antigen-binding fragment thereof, nucleic acid, vector, cell and/or pharmaceutical composition according to any of the preceding aspects in preparing a medicament or kit for treating a tumor antigen-related disease in a mammal.

[0017] The antibodies of the present disclosure can be used in a variety of applications, including detection of tumor antigens, diagnosis, treatment, or prevention of diseases associated with tumor antigens.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. **1** shows a first antigen×CD3 κλ bispecific antibodies of the present disclosure.

[0019] FIG. **2** shows binding of the humanized anti-CD3 antibody to human CD3εγ protein.

[0020] FIG. **3** shows binding of the humanized anti-CD3 antibody to a Jurkat cell.

[0021] FIG. **4** shows binding of the humanized anti-CD3 humanized antibody to human CD3εγ and cynomolgus monkey CD3εγ proteins.

[0022] FIG. **5** shows the structures of κλ001, κλ002, κλ003, κλ004, κλ005 of the present disclosure.

[0023] FIG. **6** shows the result of purification of Protein A of the anti-CD20×CD3 κλ bispecific antibody.

[0024] FIG. **7** shows the result of SEC-HPLC detection of the anti-CD20×CD3 κλ bispecific antibody.

[0025] FIG. **8** shows detection results of homodimers of anti-CD20×CD3 κλ bispecific antibody.

[0026] FIG. **9** shows binding of the anti-CD20×CD3 κλ bispecific antibody to a CD20 stably transfected cell.

[0027] FIG. **10** shows binding of the anti-CD20×CD3 κλ bispecific antibody to tumor cells SU-DHL-4, Raji and NALM-6.

[0028] FIG. **11** shows binding of the anti-CD20×CD3 κλ bispecific antibody to a Jurkat cell.

[0029] FIG. **12** shows binding of the anti-CD20×CD3 κλ bispecific antibody to a T-cell in peripheral blood.

[0030] FIG. **13** shows T-cell dependent cellular cytotoxicity (TDCC) mediated by anti-CD20×CD3 κλ bispecific antibody, FIG. **13**A shows killing of Nalm-6 cells and FIG. **13**B shows activation of T-cells.

[0031] FIG. **14** shows TDCC mediated by anti-CD20× CD3 κλ bispecific antibody, FIG. **14**A shows killing of TMD-8 cells and FIG. **14**B shows activation of T-cells.

[0032] FIG. **15** shows TDCC mediated by anti-CD20× CD3 κλ bispecific antibody, FIG. **15**A shows killing of Toledo cells and FIG. **15**B shows activation of T-cells.

[0033] FIG. **16** shows effect of anti-CD20×CD3 κλ bispecific antibody on the T-cell NFAT signaling pathway.

[0034] FIG. **17** shows inhibitory effect of the anti-CD20× CD3 κλ bispecific antibody in a xenograft model of mouse Raji with immune reconstitution.

[0035] FIG. **18** shows inhibitory effect of the anti-CD20× CD3 κλ bispecific antibody in a subcutaneous tumor model grafted by a mixture of murine Raji and human PBMC in immunodeficient mice.

[0036] FIG. **19** shows efficacy of the anti-CD20×CD3 κλ bispecific antibody in a cynomolgus monkey.

[0037] FIG. **20** shows binding of the anti-BCMA×CD3 κλ bispecific antibody to BCMA stably transfected cells.

[0038] FIG. **21** shows binding of the anti-BCMA×CD3 κλ bispecific antibody to tumor cells NCI-H929 and RPMI-8226.

[0039] FIG. **22** shows binding of the anti-BCMA×CD3 κλ bispecific antibody to a Jurkat cell.

[0040] FIG. **23** shows binding of the anti-BCMA×CD3 κλ bispecific antibody to a T-cell in the peripheral blood.

[0041] FIG. **24** shows TDCC mediated by the anti-BCMA×CD3 κλ bispecific antibody, FIG. **24**A shows killing of NCI-H929 cells and FIG. **24**B shows activation of T-cells.

[0042] FIG. **25** shows TDCC mediated by the anti-BCMA×CD3 κλ bispecific antibody, FIG. **25**A shows killing of RPMI-8226 cells and FIG. **25**B shows activation of T-cells.

[0043] FIG. **26** shows the effect of the anti-BCMA×CD3 κλ bispecific antibody on the T-cell NFAT signaling pathway.

[0044] FIG. **27** shows non-specific activation of PBMC by the anti-BCMA×CD3 κλ bispecific antibody.

[0045] FIG. **28** shows binding of the anti-BCMA×CD3 κλ bispecific antibody to an Fc receptor.

[0046] FIG. **29** shows inhibitory effect of the anti-BCMA×CD3 κλ bispecific antibody in the xenograft model of subcutaneous NCI-H929 in immunodeficient mice.

[0047] FIG. **30** shows binding of the anti-GPC3×CD3 κλ bispecific antibody to the GPC3 stably transfected cell.

[0048] FIG. **31** shows binding of the anti-GPC3×CD3 κλ bispecific antibody to a tumor cell HepG2.

[0049] FIG. **32** shows binding of the anti-GPC3×CD3 κλ bispecific antibody to the Jurkat cell.

[0050] FIG. **33** shows binding of the anti-GPC3×CD3 κλ bispecific antibody to the T-cell in the peripheral blood.

[0051] FIG. **34** shows TDCC mediated by anti-GPC3×CD3 κλ antibody, FIG. **34**A shows killing of HepG2 cells and FIG. **34**B shows activation of T-cells.

[0052] FIG. **35** shows effect of the anti-GPC3×CD3 κλ bispecific antibody on the T-cell NFAT signaling pathway.

[0053] FIG. **36** shows non-specific activation of PBMC by the anti-GPC3×CD3 κλ bispecific antibody.

[0054] FIG. **37** shows inhibitory effect of the anti-GPC3×CD3 κλ bispecific antibody in a xenograft model of a subcutaneous HepG2 in immune-reconstituted mice.

[0055] FIG. **38** shows inhibitory effect of the anti-GPC3×CD3 κλ bispecific antibody in the humanized anti-CD3 humanized murine Hepa1-6/human GPC3 xenograft model.

DETAILED DESCRIPTION OF EMBODIMENTS

[0056] In the present disclosure, the scientific and technical terms used herein have the meanings commonly understood by those skilled in the art, unless otherwise specified. Also, as used herein, protein and nucleic acid chemistry, molecular biology, cell and tissue culture, microbiology, immunology, and laboratory procedures used herein are terms and routine procedures widely used in the corresponding fields. Meanwhile, in order to better understand the present disclosure, definitions and explanations of related terms are provided below.

[0057] As used herein, a "tumor antigen" preferably refers to any antigen or antigenic determinant present in (or bound to) a tumor cell but not normally present in a normal cell, or an antigen or antigenic determinant present in or bound to a tumor cell in a greater amount than on a normal (non-tumor) cell, or an antigen or antigenic determinant present in a tumor cell in a form other than that found on a normal (non-tumor) cell. The term thus includes tumor-specific antigens, including tumor-specific antigens (TSA) or tumor-related antigens (TAA), including tumor-related membrane antigens, embryonic antigens on tumors, growth factor receptors, growth factor ligands and any other types of antigens associated with cancers. The tumor antigen can be, for example, a B-cell differentiation antigen (e.g. CD19, CD20, and CD37), a B-cell maturation antigen (B-cell maturation antigen, BCMA), a glypican 3 (GPC3), an epithelial cancer antigen (e.g. breast cancer, gastrointestinal cancer, lung cancer), a prostate-specific cancer antigen (PSA) or a prostate-specific membrane antigen (PSMA), a bladder cancer antigen, a lung (e.g. small cell lung) cancer antigen, a colon cancer antigen, an ovarian cancer antigen, a brain cancer antigen, a stomach cancer antigen, a renal cell carcinoma antigen, a pancreatic cancer antigen, a liver cancer antigen, an esophageal cancer antigen, a head and neck cancer antigen, or a colorectal cancer antigen.

[0058] TSA is (or is believed to be) unique to tumor cells and does not occur on other cells in the body (e.g. does not occur to a significant extent on other cells). TAA is not unique to tumor cells and is instead expressed on normal cells (e.g. under conditions that do not induce immune tolerance to the antigen). For example, when the immune system is immature and unable to respond, TAA may be antigens that are expressed on normal cells during fetal development, or they may be antigens that are normally present at very low levels on normal cells, but are expressed at higher levels on tumor cells.

[0059] Non-limiting examples of TSA or TAA antigens include: differentiation antigens such as MART-1/MelanA (MART-I), gp100(Pmel 17), tyrosinase, TRP-1, TRP-2 and tumor-specific multilineage antigens such as MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, p15; an overexpressed embryonic antigen, such as CEA; overexpressed oncogenes and mutated tumor suppressor genes such as p53, Ras, HER-2/neu; unique tumor antigens resulted from chromosomal translocations, such as BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR; and viral antigens such as the Epstein Barr virus antigen EBVA and the human HPV antigens E6 and E7. Other tumor antigens include TSP-180, MAGE-4, MAGE-5, MAGE-6, RAGE, NY-ESO, erbB, pl85erbB2, pl80erbB-3, c-met, nm-23H1, PSA, TAG-72, CA 19-9, CA72-4, CAM 17.1, NuMa, K-ras, β-catenin, CDK4, Mum-1, p15, p16, 43-9F, 5T4, 791Tgp 72, alpha-fetoprotein, β-HCG, BCA225, BTAA, CA125, CA15-3\CA 27.29\BCAA, CA195, CA242, CA-50, CAM43, CD68\P1, CO-029, FGF-5, G250, Ga733\EpCAM, HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB/70K, NY-CO-1, RCAS1, SDCCAG16, TA-90\Mac-2 binding protein\ cyclophilin C-related protein, TAAL6, TAG72, TLP, MUC16, IL13Rα2, FRα, VEGFR2, Lewis Y, FAP, EphA2, CEACAM5, EGFR, CA6, CA9, GPNMB, EGP1, FOLR1, endothelial receptor, STEAP1, SLC 44A4, boundin-4, AGS-16, guanidinyl cyclase C, MUC-1, CFC1B, integrin α3 chain (a3b1 chain, i.e. laminin receptor chain) and TPS. Other tumor antigens also include CD19, CD20, CD22, CD30, CD72, CD180, CD171 (L1 CAM), CD123, CD133, CD138, CD37, CD70, CD79a, CD79b, CD56, CD74, CD166, CD71, CLL-1/CLECK 12A, ROR1, BCMA, glypican3 (GPC3), mesothelin, CD33/IL3Ra, c-Met, PSCA, PSMA, glycolipid F77, EGFRvIII, GD-2, MY-ESO-1 or MAGEA3.

[0060] As used herein, the term "CD20" refers to any native CD20 from any vertebrate source including mammals, such as primates (e.g. humans) and rodents (e.g. mice and rats).

[0061] The terms "anti-CD20 antibody" and "antibody that binds CD20" refer to an antibody that is capable of binding CD20 with sufficient affinity such that the antibody is used as a diagnostic and/or therapeutic agent in targeting CD20. In one embodiment, the degree of binding of an anti-CD20 antibody to an unrelated non-CD20 protein is less than about 10% of the binding of the antibody to CD20, as measured, for example, by a radioimmunoassay (RIA). In certain embodiments, an antibody that binds CD20 has a dissociation constant (K_d) of ≤1 μM, ≤100 nM, ≤10 nM, ≤1 nM, ≤0.1 nM, ≤0.01 nM, or ≤0.001 nM (e.g. 10^{-8}M or less, e.g. 10^{-8}M to 10^{-13}M, e.g. 10^{-9}M to 10^{-13}M). In certain

embodiments, anti-CD20 antibodies bind to CD20 epitopes conserved among CD20 from different species.

[0062] As used herein, the term "BCMA" may refer to the concept of BCMA itself and any variants, isoforms and paralogs thereof, which are present together in animals and preferably in humans.

[0063] The term "human BCMA" refers to BCMA of human origin and may preferably have, but is not limited to, the amino acid sequence under Genbank accession number AB052772.1.

[0064] The terms "anti-BCMA antibody" and "antibody that binds to BCMA" refer to an antibody that is capable of binding to BCMA with sufficient affinity such that the antibody is used as a diagnostic and/or therapeutic agent in targeting BCMA. In one embodiment, the degree of binding of an anti-BCMA antibody to an unrelated non-BCMA protein is less than about 10% of the binding of the antibody to BCMA, as measured, for example, by a radioimmunoassay (RIA). In certain embodiments, an antibody that binds BCMA has a dissociation constant (K_d) of ≤1 μM, ≤100 nM, ≤10 nM, ≤1 nM, ≤0.1 nM, ≤0.01 nM, or ≤0.001 nM (e.g. 10^{-8}M or less, e.g. from 10^{-8}M to 10^{-13}M, e.g. from 10^{-9}M to 10^{-13}M). In certain embodiments, anti-BCMA antibodies bind BCMA epitopes conserved among BCMA from different species.

[0065] As used herein, the term "GPC3" may refer to the concept of GPC3 itself and any variants, isoforms and paralogs thereof, which are present together in animals and preferably in humans.

[0066] The term "human GPC3" refers to GPC3 of human origin.

[0067] The terms "anti-GPC3 antibody" and "antibody that binds GPC3" refer to an antibody that is capable of binding GPC3 with sufficient affinity such that the antibody is used as a diagnostic and/or therapeutic agent in targeting GPC3. In one embodiment, the degree of binding of an anti-GPC3 antibody to an unrelated non-GPC3 protein is less than about 10% of the binding of the antibody to GPC3 as measured, for example, by a radioimmunoassay (RIA). In certain embodiments, an antibody that binds GPC3 has a dissociation constant (K_d) of ≤1 μM, ≤100 nM, ≤10 nM, ≤1 nM, ≤0.1 nM, ≤0.01 nM, or ≤0.001 nM (e.g. 10^{-8}M or less, e.g. from 10^{-8}M to 10^{-13}M, e.g. from 10^{-9}M to 10^{-13}M). In certain embodiments, anti-GPC3 antibodies bind GPC3 epitopes conserved among GPC3 from different species. "CD3" refers to any native CD3 from any vertebrate source, including mammals, such as primates (e.g. humans), non-human primates (e.g. cynomolgus monkeys), and rodents (e.g. mice and rats), unless otherwise specified. The term encompasses "full-length" unprocessed CD3 as well as any form of CD3 derived from processing in cells. The term also encompasses naturally occurring variants of CD3, such as splice variants or allelic variants. In one embodiment, the CD3 is human CD3, in particular the epsilon subunit (CD3ε) of human CD3. The amino acid sequence of human CD3ε is shown in UniProt (www.uniprot.org) under accession number P07766 (version 144), or NCBI (www.ncbi.nlm.nih.gov/) RefSeq NP_000724.1. The amino acid sequence of *Macaca fascicularis* CD3ε is shown in NCBI GenBank no. BAB71849.1.

[0068] The use of the term "cell surface" is in accordance with its normal meaning in the art, and thus includes the exterior of a cell accessible by binding to proteins and other molecules.

[0069] As used herein, unless otherwise specified, the term "about" or "approximately" means within plus or minus 10% of a given value or range. in the case that an integer is required, the term refers to rounding up or down to the nearest integer within plus or minus 10% of the given value or range.

[0070] The phrase "substantially identical" with respect to the polypeptide sequence an antibody chain is understood to mean an antibody chain that exhibits at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or higher sequence identity to a reference polypeptide sequence. With respect to a nucleic acid sequence, the term is understood to mean a nucleotide sequence that exhibits at least greater than 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more sequence identity to a reference nucleic acid sequence.

[0071] Sequence "identity" or "homoousia" has its meanings widely acknowledged in this field, and the percentage of sequence identity between two nucleic acids or polypeptide molecules or regions can be calculated using published techniques. Sequence identity can be measured along the full length of a polynucleotide or polypeptide or along a region of the molecule. Although there are many methods of measuring identity between two polynucleotides or polypeptides, the term "identity" is well known to the skilled artisan (Carrillo, H. & Lipman, D., SIAM J Applied Math 48:1073 (1988)).

[0072] A "substitutional" variant is a variant in which at least one amino acid residue in the native sequence has been removed and inserted at its same position by a different amino acid. The substitution may be single, wherein only one amino acid in the molecule is substituted; or the substitution may be multiple, wherein the same molecule has two or more amino acids that are substituted. Multiple substitutions may be at consecutive positions. Likewise, an amino acid may be substituted with multiple residues, wherein such variants include both substitutions and insertions. An "insertional" variant is a variant in which one or more amino acids are inserted immediately adjacent to an amino acid at a particular position in a native sequence. An immediately adjacent amino acid means an amino acid attached to the α-carboxy or α-amino functional group of the amino acid. A "deletional" variant is a variant in which one or more amino acids in the native amino acid sequence have been removed. Typically, deletional variants have one or two amino acids deleted in a particular region of the molecule.

[0073] With respect to the variable domains of the antibody, the term "variable" refers to certain portions of related molecules that differ widely in sequences between antibodies, and are used for specific recognition and binding of a particular antibody to its specific target. However, the variability is not uniformly distributed throughout the variable domain of the antibody. Variability is concentrated in what is known as complementary determinant regions (CDRs, i.e. CDR1, CDR2 and CDR3) or three segments of the hypervariable region, all of which are located in the variable domains of the light and heavy chains. The more conserved portions in the variable domains are referred to as framework (FR) regions or framework sequences. Each variable domain of a native heavy and light chain comprises four FR regions predominantly in a β-folded configuration, they are joined by three CDRs, and the CDRs forms loops, the loops are joined to the β-folded structure and in some cases form

part of the β-folded structure. The CDRs of each chain are typically joined together in close proximity by FR regions and aid in the formation of antibody target binding sites (epitopes or determinants) by means of CDRs from other chains. As used herein, immunoglobulin amino acid residue numbering is performed in accordance with the immunoglobulin amino acid residue numbering system of Kabat et al., unless otherwise indicated. One CDR may have the ability to specifically bind to an associated epitope.

[0074] As used herein, an "antibody fragment" or "antigen-binding fragment" of an antibody refers to any portion of a full-length antibody that is less than full-length but comprises at least a portion of the variable region (e.g. one or more CDRs and/or one or more antibody binding sites) of the antibody that binds antigen, and thus retains binding specificity as well as at least a portion of the specific binding capacity of the full-length antibody. Thus, an antigen-binding fragment refers to an antibody fragment that comprises an antigen-binding portion that binds the same antigen as the antibody from the antibody fragment derived therefrom. Antibody fragments include antibody derivatives produced by enzymatic treatment of full-length antibodies, as well as synthetically produced derivatives, e.g. recombinantly produced derivatives. Antibodies include antibody fragments. Examples of antibody fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, single chain Fv(scFv), Fv, dsFv, diabodies, Fd and Fd' fragments and other fragments including modified fragments (see, e.g. Methods in Molecular Biology, Vol 207: Recombinant Antibodies for Cancer Therapy Methods and Protocols (2003); Chapter 1; p 3-25, Kipriyanov). The fragments may comprise multiple chains linked together, for example by disulfide bonds and/or by peptide linkers. Antibody fragments generally comprise at least or about 50 amino acids, and typically at least or about 200 amino acids. Antigen-binding fragments include any antibody fragment that, when inserted into an antibody framework (e.g. by displacement of the corresponding region), results in an antibody that immunospecifically binds (i.e. exhibits a Ka of at least or at least about 10^7-10^8M-1) an antigen. A "functional fragment" or "analog of an antibody" is a fragment or analog that prevents or substantially reduces the ability of the receptor to bind a ligand or initiate signal transduction. As used herein, functional fragments generally have the same meaning as "antibody fragments", and as far as antibodies are concerned, they may refer to fragments that prevent or substantially reduce the ability of the receptor to bind a ligand or initiate signal transduction, such as Fv, Fab, $F(ab')_2$, and the like. An "Fv" fragment consists of a dimer formed by a variable domain of a heavy chain and a variable domain of a light chain in the manner of a non-covalent association (V_H-V_L dimer). In this configuration, the three CDRs of each variable domain interact to define a target binding site on the surface of the V_H-V_L dimer, as is the case with intact antibodies. The six CDRs together confer target binding specificity to the intact antibody. However, even a single variable domain (or half of an Fv comprising only three target-specific CDRs) may still have the ability to recognize and bind targets.

[0075] As used herein, the term "bispecific antibody" (BsAb) refers to antibodies and/or antigen-binding molecules capable of specifically binding to two different antigenic determinants. Generally, a bispecific antibody and/or antigen-binding molecule comprises two antigen-binding sites, each of which is specific for a different antigenic determinant. In certain embodiments, the bispecific antibody and/or antigen-binding molecule is capable of binding two antigenic determinants simultaneously, particularly two antigenic determinants expressed on two different cells.

[0076] As used herein, "monoclonal antibody" refers to a population of identical antibodies, meaning that each individual antibody molecule in the population of monoclonal antibodies is identical to another antibody molecule. This property is in contrast to the property of a polyclonal population of the antibodies comprising antibodies having a plurality of different sequences. Monoclonal antibodies can be prepared by a number of well known methods (Smith et al. (2004) J. Clin. Pathol. 57, 912-917; and Nelson et al. J Clin Pathol(2000), 53, 111-117). For example, monoclonal antibodies can be prepared by immortalizing B cells, for example by fusion with myeloma cells to produce hybridoma cell lines or by infecting B cells with a virus, such as EBV. Recombinant techniques can also be used to prepare antibodies from clonal populations of host cells in vitro by transforming host cells with plasmids carrying artificial sequences encoding the nucleotides of the antibodies.

[0077] As used herein, the term "hybridoma" or "hybridoma cell" refers to a cell or cell line (typically a myeloma or lymphoma cell) resulted from the fusion of antibody-producing lymphocytes and non-antibody-producing cancer cells. As is known to those of ordinary skill in the art, hybridomas can be propagated and continuously supplied to produce a particular monoclonal antibody. Methods for producing hybridomas are known in the art (Harlow&Lane, 1988). When referring to the term "hybridoma" or "hybridoma cell", they also include subclones and progeny cells of hybridomas.

[0078] As used herein, a full-length antibody is an antibody having two full-length heavy chains (e.g. VH-CH1-CH2-CH3 or VH-CH1-CH2-CH3-CH4) and two full-length light chains (VL-CL) and a hinge region, e.g. an antibody naturally produced by an antibody secreting B cell as well as a synthetically produced antibody having the same domain.

[0079] The term "chimeric antibody" refers to an antibody in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, for example, an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

[0080] A "humanized" antibody refers to a form of non-human (e.g. mouse) antibody that is a chimeric immunoglobulin, immunoglobulin chain or fragment thereof (e.g. Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequence of an antibody) and contains minimal sequence derived from a non-human immunoglobulin. Preferably, the humanized antibody is a human immunoglobulin (recipient antibody) in which residues of the complementarity-determining region (CDR) of the recipient antibody are replaced by CDR residues from a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity.

[0081] Furthermore, in humanization process, it is also possible to mutate amino acid residues in the CDR1, CDR2 and/or CDR3 regions of VH and/or VL, thereby improving one or more binding properties (e.g. affinity) of the antibody. Mutations can be introduced, e.g. by PCR-mediated mutagenesis, and their effect on antibody binding or other func-

tional properties can be assessed using the in vitro or in vivo assays described herein. Typically, conservative mutations are introduced. Such mutations may be amino acid substitutions, additions or deletions. In addition, mutations in CDR typically do not exceed one or two. Thus, the humanized antibodies of the present disclosure also encompass antibodies comprising one or two amino acid mutations in CDR.

[0082] As used herein, the term "CDR" refers to a complementarity-determining region, it is known that an antibody molecule has three CDR per heavy and three CDR per light chain. CDR is also known as a hypervariable region, is present in the variable region of each of the heavy and light chains of an antibody, and has a very high site of variability in a primary structure of CDR. In the present specification, the CDR of the heavy chain is represented by CDR1, CDR2, CDR3 at the amino terminus of the amino acid sequence of the heavy chain, and the CDR of the light chain is represented by CDR1, CDR2, CDR3 at the amino terminus of the amino acid sequence of the light chain. These sites are adjacent to each other in the tertiary structure and determine the specificity of the antigen to which the antibody binds.

[0083] As used herein, the term "epitope" refers to any antigenic determinant on an antigen to which the paratope of an antibody binds. Epitopic determinants usually comprise chemically active surface types of molecules, such as amino acids or sugar side chains, and usually have specific three-dimensional structural properties and specific charge properties.

[0084] As used herein, "specific binding" or "immunospecifically binding" with respect to an antibody or antigen-binding fragment thereof may be used interchangeably herein and refers to the ability of an antibody or antigen-binding fragment to form one or more non-covalent bonds with the same antigen through non-covalent interactions between the antibody and the antibody binding site of the antigen. The antigen may be an isolated antigen or present in a tumor cell. Generally, an antibody that immunospecifically binds (or specifically binds) an antigen is the one that binds the antigen with an affinity constant (Ka) of about or of $1\times10^{7}M^{-1}$ or $1\times10^{8}M^{-1}$ or greater (or a dissociation constant (Kd) of 1×10^{-7} M or 1×10^{-8}M or less). Affinity constants can be determined by standard kinetic methods for antibody reactions, e.g. immunoassays, surface plasmon resonance (SPR) (Rich and Myszka (2000) Curr. Opin. Biotechnol 11:54; Englebienne (1998) Analyst. 123:1599), isothermal titration calorimetry (ITC), or other kinetic interaction assays known in the art. Reference can also be made to U.S. Pat. No. 7,229,619 which describes an exemplary SPR and ITC method for calculating the binding affinity of an antibody). Instruments and methods for detecting and monitoring the rate of binding in real time are known and commercially available (with reference to Malmqvist (2000) Biochem. Soc. Trans. 27:335).

[0085] As used herein, the terms "polynucleotide" and "nucleic acid molecule" refer to an oligomer or polymer comprising at least two linked nucleotides or nucleotide derivatives, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), typically linked together by phosphodiester bonds. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules and RNA molecules. The nucleic acid molecule may be single-stranded or double-stranded, and may be cDNA.

[0086] As used herein, an isolated nucleic acid molecule is a nucleic acid molecule isolated from other nucleic acid molecules present in the natural source. An "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material or culture medium when prepared by recombinant techniques, or substantially free of chemical precursors or other chemical components when chemically synthesized. Exemplary isolated nucleic acid molecules provided herein include isolated nucleic acid molecules encoding an antibody or antigen-binding fragment provided herein.

[0087] As used herein, "operably linked" with respect to a nucleic acid sequence, region, element or domain means that the nucleic acid regions are functionally related to one another. For example, a promoter may be operably linked to a nucleic acid encoding a polypeptide such that the promoter regulates or mediates transcription of the nucleic acid.

[0088] Also provided are "conservative sequence modifications" in the sequences set forth in the sequence listings described herein, i.e. nucleotide and amino acid sequence modifications that do not eliminate binding of an antibody encoded by or containing an amino acid sequence to an antigen. These conservative sequence modifications include conservative nucleotide and amino acid substitutions, and nucleotide and amino acid additions and deletions. For example, modifications can be introduced into the sequence listings described herein by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative sequence modifications include conservative amino acid substitutions in which an amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g. lysine, arginine, histidine), amino acids with acidic side chains (e.g. aspartic acid, glutamic acid), amino acids with uncharged polar side chains (e.g. glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), amino acids with nonpolar side chains (e.g. alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), amino acids with β-branched side chains (e.g. threonine, valine, isoleucine) and amino acids with aromatic side chains (e.g. tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in an anti-CD20, BCMA or GPC3 antibody is preferably replaced with another amino acid residue from the same side chain family. Methods for identifying conservative substitutions of nucleotides and amino acids that do not eliminate antigen-binding are well known in the art (see, e.g. Brumnell et al. Biochem. 32: 1180-1187 (1993); Kobayashi et al. Protein Eng. 12(10): 879-884 (1999); Burks et al. Proc. Natl. Acad. Sci. USA 94: 412-417 (1997)).

[0089] Alternatively, in another embodiment, mutations can be randomly introduced along all or a portion of the anti-GCD20, BCMA or PC3 antibody coding sequence by, for example, saturation mutagenesis, and the resulting modified anti-CD20, BCMA or GPC3 antibodies can be screened for improved binding activity.

[0090] As used herein, "expression" refers to a process of producing a polypeptide by transcription and translation of a polynucleotide. The level of expression of a polypeptide can be assessed using any method known in the art, including, for example, methods of determining the amount of polypeptide produced from a host cell. Such methods may

include, but are not limited to, quantitation of polypeptides in cell lysates by ELISA, gel electrophoresis followed by Coomassie blue staining, Lowry protein assay, and Bradford protein assay.

[0091] As used herein, a "host cell" is a cell for receiving, maintaining, replicating and expanding a vector. Host cells may also be used to express the polypeptide encoded by the vector. when the host cell divides, the nucleic acid contained in the vector replicates, thereby amplifying the nucleic acid. The host cell may be a eukaryotic cell or a prokaryotic cell. Suitable host cells include, but are not limited to, CHO cells, various COS cells, HeLa cells, HEK cells such as HEK 293 cells.

[0092] As used herein, a "vector" is a replicable nucleic acid from which one or more heterologous proteins can be expressed when the vector is transformed into an appropriate host cell. With respect to vectors, vectors include those vectors into which a nucleic acid encoding a polypeptide or fragment thereof may be introduced typically by restriction digestion and ligation. Vectors also include those comprising a nucleic acid encoding a polypeptide. Vectors are used to introduce a nucleic acid encoding a polypeptide into a host cell, to amplify the nucleic acid, or to express/display the polypeptide encoded by the nucleic acid. The vector usually remains episomal, but can be designed such that the gene or part thereof is integrated into the chromosome of the genome. Also contemplated are vectors for artificial chromosomes, such as yeast artificial vectors and mammalian artificial chromosomes. The selection and use of such vehicles are well known to those skilled in the art.

[0093] As used herein, a vector also includes a "virus vector" or a "viral vector". A viral vector is an engineered virus operably linked to a foreign gene to transfer (as a vehicle or shuttle) the foreign gene into a cell.

[0094] As used herein, an "expression vector" includes a vector capable of expressing a DNA, the DNA is operably linked to regulatory sequences such as a promoter region, and is capable of affecting the expression of such a DNA fragment. Such additional segments may include promoter and terminator sequences, and optionally may include one or more origins of replication, one or more selectable markers, enhancers, polyadenylation signals, and the like. Expression vectors are typically derived from plasmid or viral DNA, or may contain elements of both. Thus, an expression vector refers to a recombinant DNA or RNA construct, such as a plasmid, phage, recombinant virus or other vectors, when introduced into an appropriate host cell, it results in expression of a cloned DNA. Suitable expression vectors are well known to those skilled in the art and include expression vectors that are replicable in eukaryotic and/or prokaryotic cells and expression vectors that remain episomal or that are integrated into the host cell genome.

[0095] As used herein, "treating" a subject with a disease or condition means that the subject's symptoms are partially or completely alleviated or remain unchanged after treatments. Thus, the treatment includes prophylaxis, treatment and/or cure. Prevention refers to preventing the underlying disease and/or preventing the worsening of symptoms or the progression of the disease. Treatment also includes any antibody or antigen-binding fragment thereof provided and any pharmaceutical use of the compositions provided herein.

[0096] As used herein, "therapeutic effect" refers to an effect resulted from treatment of a subject that alters, typically ameliorates or ameliorates a symptom of a disease or condition, or cures a disease or condition.

[0097] As used herein, a "therapeutically effective amount" or "therapeutically effective dose" refers to an amount of a substance, compound, material, or composition comprising a compound that is at least sufficient to produce a therapeutic effect after administration to a subject. Thus, it is an amount necessary to prevent, cure, ameliorate, block, or partially block the symptoms of a disease or condition.

[0098] As used herein, a "prophylactically effective amount" or "prophylactically effective dose" refers to an amount of a substance, compound, material, or composition comprising a compound that, when administered to a subject, it has a desired prophylactic effect, e.g. preventing or delaying the occurrence or recurrence of a disease or condition, and reduces the likelihood of the occurrence or recurrence of a disease or condition. A fully prophylactically effective dose does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount can be administered in one or more administrations.

[0099] As used herein, the term "patient" refers to a mammal, such as a human.

II. Detailed Description

[0100] In one aspect, the present disclosure provides a bispecific antibody or antigen-binding fragment thereof, comprising:

[0101] (a) a first antigen-binding portion or antigen-binding fragment thereof, the first antigen-binding portion comprises a first light chain and a first heavy chain, the first light chain is a κ light chain, the first antigen-binding portion comprises a first binding domain that binds to a first antigen; and

[0102] (b) a second antigen-binding portion or antigen-binding fragment thereof, the second antigen-binding portion comprises a second light chain and a second heavy chain, the second light chain is a λ light chain, the second antigen-binding portion comprises a second binding domain that binds to a second antigen.

[0103] In some embodiments, the second antigen is a CD3 antigen.

[0104] In some embodiments, a second light chain variable region of the second antigen-binding portion has a $Gln_{40}Glu$ mutation ($V\lambda_{CD3}$: $Gln_{40}Glu$); and a second heavy chain variable region of the second antigen-binding portion has a $Gln_{39}Lys$ mutation (VH_{CD3}: $Gln_{39}Lys$).

[0105] In some embodiments, the second binding domain comprises second light chain CDRs selected from amino acid sequences of SEQ ID NOs: 7-9, 14, 15, 20, 21 or any variant thereof; and/or second heavy chain CDRs selected from amino acid sequences of SEQ ID NOs: 26-28, 31, 34, 40, 43, 46, 47 or any variant thereof.

[0106] In some embodiments, the second binding domain comprises a second light chain CDR1 selected from any of amino acid sequences of SEQ ID NOs: 7, 14 or any variant thereof, a second light chain CDR2 selected from any of amino acid sequences of SEQ ID NOs: 8, 15, 20 or any variant thereof, a second light chain CDR3 selected from any of amino acid sequences of SEQ ID NOs: 9, 21 or any variant thereof; and/or a second heavy chain CDR1 selected from any of amino acid sequences of SEQ ID NOs: 26, 31, 46 or any variant thereof, a second heavy chain CDR2 selected from any of amino acid sequences of SEQ ID NOs:

27, 47 or any variant thereof, a second heavy chain CDR3 selected from any of amino acid sequences of SEQ ID NOs: 28, 34, 37, 40, 43 of or any variant thereof.

[0107] In some embodiments, the second light chain CDRs of the second binding domain are selected from: the second light chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 7, 8, 9; the second light chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 14, 15, 9; the second light chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 7, 8, 21; the second light chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 7, 20, 21; and/or the heavy chain CDRs of the second binding domain are selected from: the second heavy chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 26, 27, 28; the second heavy chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 31, 27, 28; the second heavy chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 31, 27, 34; the second heavy chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 31, 27, 37; the second heavy chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 31, 27, 40; the second heavy chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 31, 27, 43; the second heavy chain CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 46, 47, 28.

[0108] In some embodiments, the second binding domain comprises a second light chain variable region selected from any of amino acid sequences of SEQ ID NOs: 5, 10, 12, 16, 18, 22 or any variant thereof; and/or a second heavy chain variable region selected from any of amino acid sequences of SEQ ID NOs: 24, 29, 32, 35, 38, 41, 44, 48, 50, 52 or any variant thereof.

[0109] In some embodiments, the second binding domain comprises a second light chain variable region of the amino acid sequence of SEQ ID NO: 18 or any variant thereof; and a second heavy chain variable region of the amino acid sequence of SEQ ID NO: 24 or any variant thereof.

[0110] In some embodiments, the second binding domain comprises a second light chain variable region of the amino acid sequence of SEQ ID NO: 5 or any variant thereof; and a second heavy chain variable region of the amino acid sequence of SEQ ID NO: 48 or any variant thereof.

[0111] In some embodiments, the second binding domain comprises a second light chain variable region of the amino acid sequence of SEQ ID NO: 18 or any variant thereof; and a second heavy chain variable region of the amino acid sequence of SEQ ID NO: 48 or any variant thereof.

[0112] In some embodiments, the second binding domain comprises a second light chain variable region of the amino acid sequence of SEQ ID NO: 5 or any variant thereof; and a second heavy chain variable region of the amino acid sequence of SEQ ID NO: 50 or any variant thereof.

[0113] In some embodiments, the second binding domain comprises a second light chain variable region of the amino acid sequence of SEQ ID NO: 10 or any variant thereof; and a second heavy chain variable region of the amino acid sequence of SEQ ID NO: 50 or any variant thereof.

[0114] In some embodiments, the second binding domain comprises a second light chain variable region of the amino acid sequence of SEQ ID NO: 12 or any variant thereof; and a second heavy chain variable region of the amino acid sequence of SEQ ID NO: 50 or any variant thereof.

[0115] In some embodiments, the second binding domain comprises a second light chain variable region of the amino acid sequence of SEQ ID NO: 18 or any variant thereof; and a second heavy chain variable region of the amino acid sequence of SEQ ID NO: 50 or any variant thereof.

[0116] In some embodiments, the second light chain of the second antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 58 and 66; and/or the second heavy chain of the second antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 60 and 68. In some preferred embodiments, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 58; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 60. In some preferred embodiments, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

[0117] In some embodiments, the first antigen is a tumor antigen.

[0118] In some preferred embodiments, the tumor antigen is selected from the group consisting of: CD19, CD20, CD22, CD30, CD38, CD72, CD180, CD171 (LI CAM), CD123, CD133, CD138, CD37, CD70, CD79a, CD79b, CD56, CD74, CD166, CD71, CLL-1/CLECK12A, ROR1, BCMA, GPC3, mesothelin, CD33/IL3Ra, c-Met, PSCA, PSMA, glycolipid F77, EGFRvIII, GD-2, MY-ESO-1, Her2, Her3, MUC1, MUC17, Claudin18 or MAGEA3.

[0119] In a particular embodiment, the tumor-related antigen is selected from CD20, BCMA and GPC3.

[0120] In some embodiments, the first antigen is a CD20 antigen.

[0121] In some preferred embodiments, the first light chain variable region of the first antigen-binding portion has a $Gln_{38}Lys$ mutation ($V\kappa_{CD20}$: $Gln_{38}Lys$). In some preferred embodiments, the first heavy chain variable region of the first antigen-binding portion has a $Gln_{39}Glu$ mutation (VH_{CD20}: $Gln_{39}Glu$).

[0122] In some preferred embodiments, the first light chain variable region of the first antigen-binding portion has a $Gln_{38}Lys$ mutation ($V\kappa_{CD20}$: $Gln_{38}Lys$), and the first light chain constant region has $Glu_{123}Lys$ and $Gln_{124}Lys$ mutations (Vκ-Ck_{CD20}: $Gln_{38}Lys\backslash Glu\backslash Lys\backslash Gln_{24}Lys$). In some preferred embodiments, the first heavy chain variable region of the first antigen-binding portion has a $Gln_{39}Glu$ mutation (VH_{CD20}: $Gln_{39}Glu$), and the first heavy chain constant region has $Lys_{152}Glu$ and $Lys_{218}Glu$ mutations (V_H-C_HI_{CD20}: $Gln_{39}Glu\backslash Lys_{152}Glu\backslash Lys_{218}Glu$).

[0123] In some preferred embodiments, the first light chain of the first antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 54, 62, and 70; and/or the first heavy chain of the first antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 56, 64, and 72.

[0124] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid

sequence of SEQ ID NO: 54, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 56.

[0125] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 62, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 64.

[0126] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 70, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 72.

[0127] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 54, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 56, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 58; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 60.

[0128] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 62, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 64, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 58; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 60.

[0129] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 70, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 72, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

[0130] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 62, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 64, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 58; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 60.

[0131] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 54, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 56, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

[0132] In some embodiments, the first antigen is a BCMA antigen.

[0133] In some preferred embodiments, the first light chain variable region of the first antigen-binding portion has a $Gln_{42}Lys$ mutation ($V\kappa_{BCMA}$: $Gln_{42}Lys$). In some preferred embodiments, the first heavy chain variable region of the first antigen-binding portion has a $Gln_{39}Glu$ mutation (VH_{BCMA}: $Gln_{39}Glu$).

[0134] In some preferred embodiments, the first light chain of the first antigen-binding portion is selected from the amino acid sequences of SEQ ID NOs: 80, and 84; and/or the first heavy chain of the first antigen-binding portion is selected from the amino acid sequences of SEQ ID NOs: 82 and 86.

[0135] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 80; and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 82.

[0136] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 84; and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 82.

[0137] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 80; and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 86.

[0138] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 84; and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 86.

[0139] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 80, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 82, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

[0140] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 84, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 82, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

[0141] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 80, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 86, the second light chain of the second antigen-binding portion is the amino acid sequence of amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of amino acid sequence of SEQ ID NO: 68.

[0142] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 84, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 86, the second light chain of the second

antigen-binding portion is the amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

[0143] In some embodiments, the first antigen is a GPC3 antigen.

[0144] In some preferred embodiments, the first light chain variable region of the first antigen-binding portion has $Gln_{43}Lys$ and $Gln_{39}Glu$ mutations ($V\kappa_{GPC3}$: $Gln_{43}Lys$; VH_{GPC3}: $Gln_{39}Glu$).

[0145] In some preferred embodiments, the first light chain of the first antigen-binding portion is selected from the amino acid sequences of SEQ ID NOs: 88 and 92; and/or the first heavy chain of the first antigen-binding portion is selected from the amino acid sequences of SEQ ID NOs: 90 and 94.

[0146] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 88, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 90.

[0147] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 92, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 94.

[0148] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 88, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 90, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

[0149] In some preferred embodiments, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 92, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 94, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

[0150] In some embodiments, the Fc portion of the first antigen-binding portion and/or the second antigen-binding portion of the bispecific antibody adopts a knob-into-hole structure. In some preferred embodiments, the human IgG4 knob-into-hole structure is used.

[0151] In some preferred embodiments, the first antigen-binding portion and/or the second antigen-binding portion of the bispecific antibody further has a $Ser_{228}Pro$ mutation, $Leu_{235}Glu$ mutation and/or $Pro_{329}Ala$ mutation.

[0152] In one aspect, the present disclosure provides a nucleic acid encoding the bispecific antibody or antigen-binding portion thereof described in the above.

[0153] In some preferred embodiments, the second antigen-binding portion binds to a CD3 antigen, the nucleic acid encoding the second light chain variable region of the second antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 6, 11, 13, 17, 19 and 23; and/or the nucleic acid encoding the second heavy chain variable region of the second antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 25, 30, 33, 36, 39, 42, 45, 49, 51 and 53. In some preferred embodiments, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 59 and 67; and/or the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 61 and 69. In some preferred embodiments, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 59, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 61. In some preferred embodiments, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69.

[0154] In some preferred embodiments, the first antigen-binding portion binds to a CD20 antigen, the nucleic acid encoding the first light chain variable region of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 55, 63 and 71; and/or the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 57, 65, and 73. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 55, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 57. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 63, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 65. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 71, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from a nucleotide sequence of SEQ ID NO: 73.

[0155] In some preferred embodiments, the first antigen-binding portion binds to a BCMA antigen, the nucleic acid encoding the first light chain variable region of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 81 and 85; and/or the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 83 and 87. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 81, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 83. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 85, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 83. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide

sequence of SEQ ID NO: 81, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 87. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 85, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 87.

[0156] In some preferred embodiments, the first antigen-binding portion binds to a GPC3 antigen, the nucleic acid encoding the first light chain variable region of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 89 and 93; and/or the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 91 and 95. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 89, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 91. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 93, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 95.

[0157] In some preferred embodiments, the first antigen-binding portion of the bispecific antibody binds to the CD20 antigen, the second antigen binds to the CD3 antigen, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 55, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 57, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 59, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 61. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 63, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 65, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 59, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 61. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 71, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 73, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 63, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 65, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 59, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 61. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 55, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 57, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69.

[0158] In some preferred embodiments, the first antigen-binding portion of the bispecific antibody binds to the BCMA antigen, the second antigen binds to the CD3 antigen, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 81, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 83, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 85, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 83, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 81, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 87, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 85, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is

selected from the nucleotide sequence of SEQ ID NO: 87, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69.

[0159] In some preferred embodiments, the first antigen-binding portion of the bispecific antibody binds to the GPC3 antigen, the second antigen binds to the CD3 antigen, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 89, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 91, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69. In some preferred embodiments, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 93, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 95, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69.

[0160] In one aspect, the present disclosure provides a vector comprising the nucleic acid described in the above.

[0161] In one aspect, the present disclosure provides a cell comprising the nucleic acid or vector described in the above.

[0162] In one aspect, the present disclosure provides a composition comprising the bispecific antibody or antigen-binding portion thereof, the nucleic acid, the vector and/or the cell described in the above.

[0163] In one aspect, the present disclosure provides an antibody-drug conjugate comprising the bispecific antibody or antigen-binding portions thereof covalently attached to a therapeutic moiety described in the above.

[0164] In one embodiment, the therapeutic moiety is selected from a cytotoxic moiety, a chemotherapeutic agent, a cytokine, an immunosuppressant, an immunostimulant, a lytic peptide, or a radioisotope; The antibody of the present disclosure is used as a therapeutic or diagnostic tool in diseases in which various tumor antigens are adversely expressed or found.

[0165] In one embodiment of the diseases associated with a tumor antigen, the expression of the tumor antigen in cells of the diseased tissue or organ is increased compared to the state in a healthy tissue or organ. An increase means an increase of at least 10%, in particular at least 20%, at least 50%, at least 100%, at least 200%, at least 500%, at least 1000%, at least 10000% or even more. In one embodiment, the expression is found only in diseased tissues, whereas the expression in corresponding healthy tissues is suppressed. According to the present disclosure, the diseases associated with tumor antigens include tumors.

[0166] In some embodiments, the disease associated with a tumor antigen is a CD20-related disease. In some preferred embodiments, the CD20-related disease comprises a B-cell disease, for example, a B cell proliferative disorder, in particular a CD20-positive B-cell disorder; preferably, the disease is selected from non-Hodgkin's lymphoma (NHL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and multiple myeloma (MM) and Hodgkin's lymphoma (HL).

[0167] In some embodiments, the tumor antigen-related disease is a BCMA-related disease; preferably, the BCMA-related disease includes B-cell disease; preferably, the disease is a cancer; more preferably, the cancer is a B-cell related cancer selected from multiple myeloma, malignant plasmacytoma, hodgkin's lymphoma, nodular lymphocyte-predominant Hodgkin's lymphoma, Kahler's disease and myeloid leukemia, plasma cell leukemia, plasmacytoma, B-cell prolymphocytic leukemia, hairy cell leukemia, B-cell non-Hodgkin's lymphoma (NHL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), follicular lymphoma, burkitt lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, precursor B-lymphocyte lymphoma, myeloid leukemia, waldenstrom's macroglobulinemia, diffuse large B cell lymphoma, follicular lymphoma, marginal zone lymphoma, mucosa-related lymphoid tissue lymphoma, small cell lymphocytic lymphoma, mantle cell lymphoma, burkitt lymphoma, primary mediastinal (thymic) large B cell lymphoma, lymphoplasmacytic lymphoma, waldenstrom's macroglobulinemia, lymph node marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, large B-cell lymphoma rich in T-cells/histiocytes, primary central nervous system lymphoma, primary cutaneous diffuse large B-cell lymphoma (leg type), elderly EBV-positive diffuse large B-cell lymphoma, inflammation-related diffuse large B-cell lymphoma, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablast-cell lymphoma, large B-cell lymphoma arising in HHV8-related multicenter Castleman's disease, unclassified B-cell lymphoma with intermediate features between diffuse large B-cell lymphoma and Burkitt's lymphoma, unclassified B-cell lymphoma with intermediate features between diffuse large B-cell lymphoma and classic Hodgkin's lymphoma, and other B-cell-related lymphomas; more preferably, the B-cell disease is a B-cell disorder; preferably, the plasma cell disorder is selected from: multiple myeloma, plasmacytoma, plasma cell leukemia, macroglobulinemia, amyloidosis, waldenstrom's macroglobulinemia, solitary plasmacytoma of the bone, extramedullary plasmacytoma, osteosclerotic myeloma, heavy chain disease, monoclonal gammopathy of unclear significance, and multiple myeloma of stasis type; preferably, the disease is an autoimmune disease such as systemic lupus erythematosus or rheumatoid arthritis.

[0168] In some embodiments, the therapeutic agent comprises an antibody that specifically binds to an activated T-cell antigen.

[0169] In one embodiment, the therapeutic agent comprises an antibody that specifically binds CD3, particularly CD3 epsilon.

[0170] A method of treating diseases and conditions by using bispecific antibodies of the present disclosure include the steps of: administering to the mammal a therapeutically

effective amount of the antibody or antigen-binding fragment thereof or the nucleic acid molecule or vector or cell or pharmaceutical composition according to any of the preceding aspects.

[0171] In some embodiments, the disclosure provides a method of treating or preventing a cancer disease comprising administering to a patient an antibody capable of binding to GPC3, wherein the antibody is administered to provide a serum level of at least 40 μg/ml. In various embodiments, the antibody is administered to provide a serum level of at least 50 μg/ml, at least 150 μg/ml, at least 300 μg/ml, at least 400 μg/ml, or at least 500 μg/ml. In various embodiments, the antibody is administered to provide a serum level of no more than 800 μg/ml, 700 μg/ml, 600 μg/ml, 550 μg/ml, or 500 μg/ml. In one embodiment, the serum level provided is from 40 μg/ml to 700 μg/ml, preferably from 40 μg/ml to 600 μg/ml, preferably from 50 μg/ml to 500 μg/ml, such as from 150 μg/ml to 500 μg/ml or from 300 μg/ml to 500 μg/ml. The term "serum level" as used in the present description means the concentration of the discussed substance in serum. In one embodiment, serum levels are provided for at least 7 days or at least 14 days. In one embodiment, the method comprises administering a dose of antibody of at least 300 mg/m^2, for example, at least 600 mg/m^2, and preferably at most 1500 mg/m^2, at most 1200 mg/m^2 or at most 1000 mg/m^2.

[0172] In some embodiments, the disclosure provides a method of treating or preventing a cancer disease comprising administering to a patient an antibody capable of binding to GPC3, wherein the antibody is administered at a dose of at least 300 mg/m^2, such as at least 600 mg/m^2, and preferably at most 1500 mg/m^2, at most 1200 mg/m^2, or at most 1000 mg/m^2.

[0173] In some embodiments, the disclosure provides a method of treating or preventing a cancer disease comprising administering to a patient an antibody capable of binding to GPC3, wherein at least 50%, preferably 60%, 70%, 80% or 90% of the cancer cells of the patient are positive for GPC3, and/or at least 40%, preferably 50% or 60% of the cancer cells of the patient are positive for surface expression of GPC3. In this aspect, the present disclosure also provides a method of treating or preventing a cancer disease, the method comprising: a. identifying patients showing at least 50%, preferably 60%, 70%, 80% or 90% of GPC3-positive cancer cells and/or at least 40%, preferably 50% or 60% of cancer cells that are positive for surface expression of GPC3; and b. administering to the patient an antibody capable of binding GPC3. In one embodiment, at least 95% or at least 98% of the cancer cells of the patient are GPC3-positive. In one embodiment, at least 70%, at least 80%, or at least 90% of the cancer cells of the patient are positive for surface expression of GPC3.

[0174] In one embodiment of the methods of any of the aspects herein, the therapeutic outcome of the cancer disease is to achieve stable disease conditions. In one embodiment, stable disease condition is achieved for at least 2 months, at least 3 months, or at least 6 months.

[0175] In some embodiments, the present disclosure provides methods of achieving stable disease condition in a cancer patient comprising administering to the patient an antibody capable of binding GPC3. In one embodiment, stable disease condition is achieved for at least 2 months, at least 3 months, or at least 6 months.

[0176] In one embodiment of the methods of any aspect herein, the antibody is administered in a single dose or multiple doses.

[0177] In some embodiments, the disclosure provides a method of treating or preventing a cancer disease comprising administering to a patient an antibody capable of binding to GPC3, wherein the antibody is administered in multiple doses.

[0178] If the antibody is administered in multiple doses according to the present disclosure, the antibody is preferably administered in at least 3 doses, at least 4 doses, at least 5 doses, at least 6 doses, at least 7 doses, at least 8 doses, at least 9 doses, or at least 10 doses and preferably at most 30 doses, 25 doses, 20 doses, 15 doses, or 10 doses. Preferably, the dose of antibody is administered at intervals of at least 7 days, at least 10 days, at least 14 days, or at least 20 days. The dose of antibody is preferably administered at intervals of from 7 to 30 days, from 10 to 20 days and preferably about 14 days.

[0179] In one embodiment, the antibody is administered so as to provide a serum level of at least 40 μg/ml. In various embodiments, the antibody is administered to provide a serum level of at least 50 μg/ml, at least 150 μg/ml, at least 300 μg/ml, at least 400 μg/ml, or at least 500 μg/ml. In various embodiments, the antibody is administered to provide a serum level of no more than 800 μg/ml, 700 μg/ml, 600 μg/ml, 550 μg/ml, or 500 μg/ml. In one embodiment, the serum level provided is from 40 μg/ml to 700 μg/ml, preferably from 40 μg/ml to 600 μg/ml, preferably from 50 μg/ml to 500 μg/ml, such as from 150 μg/ml to 500 μg/ml or from 300 μg/ml to 500 μg/ml. In one embodiment, serum levels are provided for at least 7 days or at least 14 days. In one embodiment, the method comprises administering a dose of at least 300 mg/m^2, such as at least 600 mg/m^2 and preferably at most 1500 mg/m^2, at most 1200 mg/m^2 or at most 1000 mg/m^2 of the antibody.

[0180] Use of the antibody or antigen-binding fragment thereof or the nucleic acid molecule or the vector or the cell or the pharmaceutical composition according to any of the preceding aspects in the manufacture of a medicament for the treatment of a GPC3-related disease in a mammal.

[0181] According to any of the preceding aspects, optionally, the antibody is conjugated to other drugs, such as a labeled or cytotoxic conjugate.

[0182] In one aspect, the disclosure also includes kits, e.g. kits comprising the antibodies, fragments thereof, homologues, derivatives thereof, nucleic acids, vectors, cells, compositions, etc. of the disclosure, e.g. a labeled or cytotoxic conjugate, as well as instructions for use of the antibody, a conjugate that kills a particular type of cell, etc. The instructions can include directions for using the antibody, conjugate, etc. in vitro, in vivo, or ex vivo. The antibody may be in liquid form or in solid form, usually lyophilized. The kit may contain other suitable reagents, such as buffers, reconstitution solutions and other necessary components for the intended uses. Combinations of reagents packaged in predetermined amounts with instructions for their use, e.g. for therapeutic use or for conducting diagnostic assays, are contemplated. When the antibody is labeled, e.g. with an enzyme, then the kit can include a substrate and cofactors required for the enzyme (e.g. a substrate precursor providing a detectable chromophore or fluorophore). In addition, other additives such as stabilizers, buffers (e.g. blocking buffers or lysis buffers), and the like may also be

included. The relative amounts of the various reagents can be varied to provide a concentrate of a reagent solution, which provides user flexibility, space savings, reagent savings, etc. These reagents may also be provided in dry powder form, usually in lyophilized form, including excipients which, when dissolved, provide a reagent solution having the appropriate concentration.

[0183] Use of the antibody or functional fragment thereof or the nucleic acid molecule or the vector or the cell or the pharmaceutical composition or the kit according to any of the preceding aspects for the preparation of an agent for inhibiting GPC3 binding.

[0184] In addition, the antibodies of the present disclosure can be used in immunoassays, purification methods, and other methods using immunoglobulins or fragments thereof. Such uses are well known in the art.

[0185] Accordingly, the present disclosure also provides compositions comprising the anti-GPC3 antibodies of the present disclosure, or fragments thereof, conveniently combined with a pharmaceutically acceptable carrier, diluent or excipient, as is conventional in the art.

[0186] As used in this disclosure, the term "pharmaceutical composition" refers to formulations of various preparations. Formulations containing therapeutically effective amounts of multivalent antibodies are in sterile liquid solution, liquid suspension, or lyophilized form, optionally containing stabilizers or excipients.

[0187] The antibodies of the present disclosure can be used as a composition administered alone, or can be used in combination with other active agents.

[0188] In some embodiments, the humanized antibodies of the disclosure are conjugated to a therapeutic moiety (i.e. a drug). The therapeutic moiety can be, for example, a cytotoxin, a chemotherapeutic agent, a cytokine, an immunosuppressant, an immunostimulant, a lytic peptide, or a radioisotope. Such conjugates are referred to herein as "antibody-drug conjugates" or "ADC".

[0189] In some embodiments, the antibody is conjugated to a cytotoxic moiety. The cytotoxic moiety may for example be selected from: paclitaxel; cytochalasin B; gramicidin D; ethidium bromide; emetine; mitomycin; etoposide; teniposide; vincristine; vinblastine; colchicine; doxorubicin; daunorubicin; dihydroxy anthracenedione; tubulin inhibitors such as maytansine or analogs or derivatives thereof; antimitotic agents such as monomethyl auristatin E or F or analogues or derivatives thereof; hareotoxin 10 or 15 or an analogue thereof; irinotecan or an analog thereof; mitoxantrone; mithramycin; actinomycin D; 1-dehydrotestosterone; glucocorticoids; procaine; tetracaine; lidocaine; propranolol; puromycin; calicheamicin or an analogue or derivative thereof; antimetabolites such as methotrexate, 6 mercaptopurine, 6 thioguanine, cytarabine, fludarabine, 5 fluorouracil, decadiazine, hydroxyurea, asparaginase, gemcitabine or cladribine; alkylating agents such as mechlorethamine, thiopurine, chlorambucil, melphalan, BSNU, CCNU, cyclophosphamide, busulfan, dibromomanmitol, streptozotocin, DTIC, procarbazine, mitomycin C; platinum derivatives such as cisplatin or carboplatin; duocarmycin A, duocarmycin SA, rapamycin (CC-1065) or analogs or derivatives thereof; antibiotics such as actinomycin, bleomycin, daunorubicin, doxorubicin, idarubicin, mithramycin, mitomycin, mitoxantrone, plicomycin, AMC; pyrrolo [2, 1-c] [1, 4]-benzodiazepine(PDB); diphtheria toxins and related molecules such as diphtheria A chain and active fragments and hybrid molecules thereof, ricin toxins such as ricin A or deglycosylated ricin A chain toxins, cholera toxins, shiga-like toxins such as SLT I, SLT II, SLT IIV, LT toxins, C3 toxins, shiga toxins, pertussis toxins, tetanus toxins, soybean Bowman-Birk protease inhibitors, *pseudomonas* exotoxin, arolin, saporin, modeccin, gelsolin, abrin A chain, modeccin A chain, α-sarcin, *Aleurites fordii* proteins, caryophyllin proteins, pokeweed proteins such as PAPI, PAPII and PAP-S, *Momordica charantia* inhibitors, curcin, crotin, *Sapaonaria officinalis* inhibitors, gelonin, mitomycin, restrictocin, phenomycin and enomycin toxins; RNase; DNase I, staphylococcal endotoxin A; pokeweed antiviral protein; diphtheria toxin and *pseudomonas* endotoxin.

[0190] In some embodiments, the antibody is conjugated to auristatin or a peptide analog, derivative or prodrug thereof. It has been shown that auristatin interferes with microtubule dynamics, GTP hydrolysis and nuclear and cell division and has anti-cancer and anti-fungal activity. For example, auristatin E can be reacted with p-acetylbenzoic acid or benzoylpentanoic acid to produce AEB and AEVB, respectively. Other typical auristatin derivatives include AFP, MMAF (monomethyl auristatin F) and MMAE (monomethyl auristatin E). Suitable auristatins and analogs, derivatives, and prodrugs of auristatins, as well as suitable linkers for conjugating auristatins to Ab, are described, for example, in U.S. Pat. Nos. 5,635,483, 5,780,588, and 6,214,345, and International Patent Application Publication Nos. WO02088172, WO2004010957, WO2005081711, WO2005084390, WO2006132670, WO03026577, WO200700860, WO207011968, and WO205082023.

[0191] In some embodiments, the antibody is conjugated to a pyrrolo [2, 1-c] [1, 4]-benzodiazepine (PDB) or a peptide analog, derivative or prodrug thereof. Suitable PDB and PDB derivatives and related art are described, for example, in Hartley J. A. et al. Cancer Res 2010; 70(17): 6849-6858; antonow D. et al. Cancer J 2008; 14(3): 154-169; howard P. W. et al. Bioorg Med Chem Lett 2009; 19: 6463-6466 and Sagnou et al. Bioorg MedChem Lett 2000; 10(18): 2083-2086.

[0192] In some embodiments, the antibody is conjugated to a cytotoxic moiety selected from: anthracyclines, maytansinoids, calicheamicins, duocarmycins, rapamycin (CC-1065), dolastatin 10, dolastatin 15, irinotecan, monomethyl auristatin E, monomethyl auristatin F, PDB, or any analog, derivative or prodrug thereof.

[0193] In some embodiments, the antibody is conjugated to an anthracycline or an analog, derivative or prodrug thereof. In some embodiments, the antibody is conjugated to maytansine or an analog, derivative or prodrug thereof. In some embodiments, the antibody is conjugated to a calicheamicin or an analog, derivative or prodrug thereof. In some embodiments, the antibody is conjugated to a duocarmycin or an analog, derivative or prodrug thereof. In some embodiments, the antibody is conjugated to rapamycin (CC-1065) or an analog, derivative or prodrug thereof. In some embodiments, the antibody is conjugated to haremomycin 10 or an analog, derivative or prodrug thereof. In some embodiments, the antibody is conjugated to haremomycin 15 or an analog, derivative or prodrug thereof. In some embodiments, the antibody is conjugated to monomethyl auristatin E or an analog, derivative or prodrug thereof. In some embodiments, the antibody is conjugated to monomethyl auristatin F or an analog, derivative or prodrug

thereof. In some embodiments, the antibody is conjugated to a pyrrolo [2, 1-c] [1, 4]-benzodiazepine or an analog, derivative or prodrug thereof. In some embodiments, the antibody is conjugated to irinotecan or an analog, derivative or prodrug thereof.

[0194] In some embodiments, the antibody is conjugated to a cytokine (e.g. IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, IL-18, IL-23, IL-24, IL-27, IL-28a, IL-28b, IL-29, KGF, IFNa, IFN3, IFNy, GM-CSF, CD40L, Flt3 ligand, stem cell factor, ancestine, and TNFa).

[0195] In some embodiments, the antibody is conjugated to a radioisotope or a chelate containing a radioisotope. For example, the antibody can be conjugated to a chelator linker (e.g. DOTA, DTPA, or tixistan) that allows the antibody to complex with the radioisotope. The antibody may also or alternatively comprise or be conjugated to one or more radiolabeled amino acids or other radiolabeled molecules. Non-limiting examples of radioisotopes include ^{3}H, ^{14}C, ^{15}N, ^{35}S, $90Y$ ^{99}Tc, ^{125}I, ^{131}I, ^{186}Re, ^{213}Bi, ^{225}Ac, and ^{227}Th. For therapeutic purposes, radioisotopes emitting β or α particle radiation may be used, such as ^{131}I, ^{90}Y, ^{211}At, ^{212}Bi, ^{67}Cu, ^{186}Re, ^{188}Re and ^{212}Pb.

[0196] Techniques for conjugating molecules to antibodies are well known in the art. Typically, the nucleic acid molecule is covalently linked to a lysine or cysteine on the antibody via an N-hydroxysuccinimide ester or maleimide functional group, respectively. Conjugation methods using engineered cysteines or incorporating unnatural amino acids have been reported to improve homogeneity of conjugates. In particular, one skilled in the art may also contemplate generating reactive endogenous glutamine-engineered Fc-containing polypeptides with acyl donor glutamine-containing tags (e.g. Gin peptide-containing tags or Q-tags) or by polypeptide engineering (e.g. by amino acid deletions, insertions, substitutions, or mutations in the polypeptide). Transglutaminase can then be covalently cross-linked with an amine donor agent (e.g. a small molecule comprising or linked to a reactive amine) to form a stable and homogeneous population of engineered Fc-containing polypeptide conjugates, wherein the amine donor agent is site-specifically conjugated to the Fc-containing polypeptide through an acyl-donor glutamine-containing tag or an accessible/exposed/reactive endogenous glutamine (WO2012059882).

[0197] It will be appreciated that the therapeutic agents according to the foregoing embodiments will be administered with suitable pharmaceutically acceptable carriers, excipients, and other agents incorporated into the formulation to provide improved transfer, delivery, tolerability, etc. These formulations include, for example, powders, pastes, ointments, gels, waxes, oils, lipids, lipid-containing (cationic or anionic) carriers (e.g. Lipofectin™), DNA conjugates, anhydrous syrups, oil-in-water and water-in-oil emulsions, emulsion polyethylene glycols (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing polyethylene glycol. Any of the foregoing mixtures may be suitable for treatment or therapy according to the present disclosure, provided that the active ingredients in the formulation are not inactivated by the formulation and that the formulation is physiologically compatible and tolerates the route of administration.

[0198] In one embodiment, the antibodies described above can be used as therapeutic agents. Such agents will generally be used to treat, alleviate and/or prevent a disease or pathology associated with abnormal tumor antigen expression, activity and/or signaling in a subject. A treatment regimen can be performed using standard methods by identifying a subject, e.g. a human patient, having (or at risk of or developing) a disease or disorder associated with aberrant tumor antigen expression, activity, and/or signaling, e.g. a tumor antigen-related disorder. An antibody preparation, preferably one with high specificity and affinity for its target antigen, is administered to a subject and will generally have an effect due to its binding to the target. The administered antibody can eliminate or inhibit or interfere with the expression, activity and/or signaling function of the target (e.g. tumor antigen). The administered antibody can eliminate or inhibit or interfere with the binding of the target (e.g. tumor antigen) to its endogenous ligand to which it naturally binds. For example, an antibody binds to a target and modulates, blocks, inhibits, reduces, antagonizes, neutralizes, and/or otherwise interferes with tumor antigen expression, activity, and/or signaling.

[0199] In some embodiments, to treat a disease or disorder associated with aberrant tumor antigen expression, antibodies having heavy and light chain CDR can be administered to a subject.

[0200] In another embodiment, antibodies directed against tumor antigens can be used in methods known in the art to correlate tumor antigen localization and/or quantitation (e.g. for determining tumor antigen and/or levels of tumor antigen in an appropriate physiological sample, for diagnostic methods, for protein imaging, etc.). In a given embodiment, an antibody having specificity for a tumor antigen or a derivative, fragment, analog and comprising an antigen-binding domain derived from the antigen, is used as a pharmaceutically active compound (hereinafter referred to as "therapeutic agent").

[0201] In another embodiment, antibodies specific for tumor antigens can be used to isolate tumor antigen polypeptides by standard techniques such as immunoaffinity, chromatography or immunoprecipitation. Antibodies (or fragments thereof) directed against a tumor antigen protein can be used to detect the protein in a biological sample. In some embodiments, tumor antigens can be detected in a biological sample as part of a clinical testing procedure, for example, to determine the efficacy of a given treatment regimen. Detection may be facilitated by conjugating (i.e. physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazine aminofluorescein, dansyl chloride, or phycoerythrin; one example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin and aequorin, and examples of suitable radioactive materials include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

[0202] In another embodiment, antibodies according to the present disclosure can be used as reagents for detecting the presence of tumor antigens or protein fragments thereof in a sample. In some embodiments, the antibody comprises a detectable label. The antibody is a polyclonal antibody, or more preferably a monoclonal antibody. Whole antibodies or

fragments thereof (e.g. Fab, scFv or $F(ab')_2$) are used. The term "labeling" in reference to an antibody is intended to encompass direct labeling of the antibody by conjugating (i.e. physically linking) a detectable substance to the antibody, as well as indirect labeling of the antibody by reaction with another reagent that is directly labeled. Examples of indirect labeling include detection of the first antibody using a fluorescently labeled second antibody, and end-labeling of the antibody with biotin to enable detection with fluorescently labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present in a subject. Thus, the term "biological sample" as used includes blood and fractions or components of blood, including serum, plasma, or lymph. In other words, the detection method of the foregoing embodiments can be used to detect the analyte mRNA, protein or genomic DNA in a biological sample in vitro as well as in vivo. For example, analyte mRNA in vitro detection techniques include Northern hybridization and in situ hybridization. In vitro techniques for detection of analyte proteins include enzyme-linked immunosorbent assays (ELISA), Western blots, immunoprecipitations, and immunofluorescence. Analyte genomic DNA in vitro detection techniques include Southern hybridization. Procedures for performing immunoassays are described, for example, in "ELISA: Theory and Practice: Methods in Molecular Biology, vol. 42, J. R. Crowther (ed.) Human Press, totowa, N. J. 1995. In addition, in vivo techniques for detection of an analyte protein include introducing into a subject a labeled anti-analyte protein antibody. For example, an antibody can be labeled with a radiolabel, and the presence and location of the radiolabel in the subject can then be detected by standard imaging techniques.

[0203] The antibodies described herein and derivatives, fragments, analogs, and homologs thereof can be incorporated into pharmaceutical compositions suitable for administration. The principles and considerations involved in preparing such compositions and guidelines for selecting components are well known in the art.

[0204] Such compositions typically comprise the antibody and a pharmaceutically acceptable carrier. When antibody fragments are used, minimal inhibitory fragments that specifically bind to the target protein binding domain may be preferred. For example, based on the variable region sequence of an antibody, peptide molecules can be designed that retain the ability to bind to a target protein sequence. Such peptides can be chemically synthesized and/or produced by recombinant DNA techniques (see, e.g. Marasco et al. Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993)).

[0205] As used herein, the term "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable pharmaceutically acceptable carriers are described in the latest edition of Remington's Pharmaceutical Sciences, a standard reference text in the art, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils can also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the antibody, its use in the compositions is contemplated.

[0206] The pharmaceutical compositions of the foregoing embodiments are formulated to be compatible with their intended route of administration. Examples of routes of administration include parenteral, e.g. intravenous, intradermal, subcutaneous, oral (e.g. inhalation), transdermal (i.e. topical), transmucosal, and rectal administration. Solutions or suspensions for parenteral, intradermal or subcutaneous administration may include the following components: sterile diluents for injection such as water, saline solutions, fixed oils, polyethylene glycols, glycerol, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as Ethylene Diamine Tetraacetic Acid (EDTA); buffers, such as acetates, citrates or phosphates, and agents to adjust the osmotic pressure, such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0207] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable pharmaceutically acceptable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (such as glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0208] Sterile injectable solutions can be prepared by incorporating the antibody in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the antibody into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields

a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution of such ingredients.

[0209] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressurized container or dispenser that contains a suitable propellant, such as a gas, for example carbon dioxide, or a nebulizer.

[0210] Systemic administration may also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, one or more of the antibodies can be formulated into ointments, salves, gels, or creams as generally known in the art.

[0211] The compounds may also be prepared in the form of suppositories (e.g. with conventional suppository bases such as cocoa butter or other glycerides) or retention enemas for rectal delivery.

[0212] In one embodiment, the antibody may be prepared with carriers that prevent rapid elimination from the body, such as sustained/controlled release formulations, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparing such formulations will be apparent to those skilled in the art.

[0213] It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form, as used herein, refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit contains a predetermined quantity of one or more antibodies calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the foregoing embodiments are dictated by and directly dependent on: the unique characteristics of antibodies and the specific therapeutic effects to be achieved, and the limitations inherent in the art of formulating such antibodies for treating individuals.

[0214] The pharmaceutical compositions can be presented in a container, pack, or dispenser together with instructions for administration.

[0215] The formulations described herein may also contain more than one antibody depending on the particular situation to be treated, preferably those which have complementary activities but do not adversely affect each other. Alternatively or additionally, the composition may, for example, comprise an agent that enhances its function, such as a cytotoxic agent, a cytokine, a chemotherapeutic agent, or a growth inhibitor. Such molecules are suitably present in combination in amounts effective for the intended purpose. For example, they may be present in combination in a kit or in combination for use.

[0216] In one embodiment, one or more antibodies can be administered in combination therapy, i.e. in combination with other agents such as therapeutic agents that can be used to treat pathological conditions or disorders, such as various forms of cancer, autoimmune disorders, and inflammatory diseases. The term "in combination" means herein that the agents are administered substantially synchronously, simultaneously or sequentially. If administered sequentially, the first of the two compounds is still preferably detected at an effective concentration at the treatment site when the second compound is initially administered. In one instance, a "combination" can also include both an antibody of the present disclosure and another therapeutic agent in a kit.

[0217] For example, combination therapy can comprise coformulation and/or coadministration of one or more antibodies described herein with one or more additional therapeutic agents (e.g. one or more cytokine and growth factor inhibitors, immunosuppressants, anti-inflammatory agents, metabolic inhibitors, enzyme inhibitors, and/or cytotoxic or cytostatic agents, as described in more detail below). Such combination therapy may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with each monotherapy.

[0218] In one embodiment, the treatment regimen is effective to reduce cytokine release associated with administration of the T-cell activating therapeutic agent in the subject as compared to a corresponding treatment regimen without administration of an anti-tumor antigen antibody.

[0219] For purposes of clarity and conciseness, features are described herein as part of the same or separate embodiments. However, it will be understood that the scope of the disclosure may include some embodiments having a combination of all or some of the features described.

[0220] FIG. **1** shows the structure of a novel primary antigen×CD3 κλ bispecific antibody.

[0221] The experiments of the present disclosure demonstrate that in the case of free combination, the λ light chain of the humanized CD3 arm tends to pair with the homologous heavy chain at a lower pairing ratio with the heterologous heavy chain; similarly, the κ light chain of the humanized antigen arm also tends to pair with the homologous heavy chain, with a very low pairing ratio with the humanized CD3 heavy chain; at the same time, the introduction of complementary charge variants in the Fv further reduces the potential for light chain mismatches. The Fc portion of the anti-CD20×CD3 κλ bispecific antibody adopts the human IgG4 knob-into-hole structure, and stabilizes the hinge region and reduces interaction with Fcγ receptors as well as C1q by mutating $Ser_{228}Pro$, $Leu_{235}Glu$ and $Pro_{329}Ala$.

EXAMPLES

Example 1: Optimization of Anti-CD3 Antibody and Activation of T-Cells

1. Synthesis of Recombinant Proteins

[0222] The nucleotide sequences of the extracellular regions of human CD3γ (UniProt P09693, gln23-Asn116) and CD3ε (UniProt P07766, gln23-Asp126) were synthesized, fused with human IgG Fc hole or Fc knob respectively at the C-terminus, and expressed to form a human CD3εγ-Fc heterodimer (the amino acid sequence of human CD3γ IgG Fc (hole) is shown in SEQ ID NO. 1, and the amino acid sequence of human CD3ε IgG Fc (knob) is shown in SEQ ID NO. 2); cynomolgus monkey CD3γ (UniProt Q 95LI7, gln23-Asn110) and CD3ε (UniProt Q 95LI5, gln22-Asp117) were also synthesized, C-terminally fused to Cynomolgus monkey IgG Fc hole or Fc knob, respectively, and expressed

to form a Cynomolgus monkey CD3εγ-Fc heterodimer (the amino acid sequence of Cynomolgus monkey CD3γ IgG Fc (hole) is shown in SEQ ID NO. 3, and the amino acid sequence of Cynomolgus monkey CD3γ IgG Fc (knob) is shown in SEQ ID NO. 4). Recombinant plasmids expressing CD3γ-Fc and CD3ε-Fc were mixed with 3 mg/mL PEI (Polysciences, #24765-2) and co-transfected into HEK 293E cells (culture medium OPM-293 CD03 DPM). After 7 days at 37° C. in 120 rpm 5% CO_2, the supernatant of culture medium was collected and purified by Protein A affinity chromatography to obtain recombinant CD3εγ-Fc protein of human or cynomolgus monkeys.

2. Humanization of CD3 Antibody

[0223] Mouse hybridoma CD3 antibody (EMBO J. 1985.4 (2): 337-344; J. Immunol. 1986, 137(4): 1097-100; J. Exp. Med. 1991, 174: 319-326; J. Immunol. 1991, 147(9): 3047-52) recognizes the human and cynomolgus monkey CD3 receptor, the sequence of which is as follows.

The amino acid sequence of the light chain of anti-CD3 murine monoclonal antibody (SEQ ID NO. 96):

QAVVTQESALTTSPGETVTLTCR**SSTGAVTTSNYAN**

WVQQKPDHLFTGLIG**GTNKRAP**GVPARFSGSLIGDK

AALTITGAQTEDEAIYFCA**LWYSNLWV**FGGGTKLTVL

The amino acid sequence of the heavy chain of anti-CD3 murine monoclonal antibody (SEQ ID NO. 97):

-continued

EVQLVESGGGLVQPKGSLKLSCAASGFTFN**TYAMNW**

VRQAPGKGLEWVAR**IRSKYNNYATYYADS**VKDRFTI

SRDDSQSILYLQMNNLKTEDTAMYYCVR

HGNFGNSYVSWFAYWGQGTLVTVSS

[0224] The anti-CD3 murine monoclonal antibody was humanized, the human germline gene IMGT_hVL7-43 with the highest homology was selected for light chain CDR transplantation, and human IGLJ3*02 was selected for FM4; human IMGT hVH3-73 was selected for heavy chain CDR grafting and human IGHJ4*01 for FM4. Different heavy and light chain variants were designed (Table 1).

TABLE 1

Variable region sequences of humanized anti-CD3 antibodies

	SEQ ID Nos. 5-23				
Light chain variable region of CD3 humanized antibody	LCVR		LCDR1	LCDR2	LCDR3
	Amino acid sequence	Nucleotide sequence	Amino acid sequence	Amino acid Sequence	Amino acid Sequence
hVL1	5	6	7	8	9
hVL2	10	11	7	8	9
hVL3	12	13	14	15	9
hVL4	16	17	14	15	9
hVL5	18	19	7	8	21
hVL6	22	23	7	20	21
	SEQ ID Nos. 24-53				
Heavy chain variable region of CD3 humanized antibody	HCVR		HCDR1	HCDR2	HCDR3
	Amino acid sequence	Nucleotide sequence	Amino acid Sequence	Amino acid Sequence	Amino acid Sequence
hVH1	24	25	26	27	28
hVH2	29	30	31	27	28
hVH3	32	33	31	27	34
hVH4	35	36	31	27	37
hVH5	38	39	31	27	40
hVH6	41	42	31	27	43
hVH7	44	45	46	47	28
hVH8	48	49	26	27	28
hVH9	50	51	26	27	28
hVH10	52	53	26	27	28

[0225] The amino acid sequence of hVL1 is shown in SEQ ID NO. 5, nucleic acid encoding the same is shown in SEQ ID NO. 6, and LCDR1, LCDR2 and LCDR3 thereof are shown in SEQ ID NOs. 7, 8 and 9 respectively.

QAVVTQEPSLTVSPGGTVTLTC**RSSTGAVTTSNYAN**

WVQQKPGQAPRGLI**GGTNKRAP**WTPARFSGSLLGGKAA

LTLSGAQPEDEAEYYC**ALWYSNLWV**FGGGTKLTVL

Nucleic acid sequence
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTCCTGG

CGGCACAGTGACCCTGACCTGTAGATCTTCTACAG

GCGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGCAGAAG

CCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAAC

AAACAAGAGAGCCCCTTGGACACCCGCCAGATTCTCTGGATCTC

-continued

TGCTCGGCGGAAAGGCCGCTCTGACACTTTCTGGT

GCTCAGCCTGAGGACGAGGCCGAGTACTATTGTGCCCTGTGGTA

CAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAAC

TGACAGTTCTG

[0226] The amino acid sequence of hVL2 is shown in SEQ ID NO. 10, nucleic acid encoding the same is shown in SEQ ID NO. 11, and LCDR1, LCDR2 and LCDR3 thereof are shown in SEQ ID NOs. 7, 8 and 9, respectively.

QAVVTQEPSLTVSPGGTVTLTC**RSSTGAVTTSNYAN**

WVQEKPGQAPRGLI**GGTNKRAP**WTPARFSGSLLGGKAA

LTLSGAQPEDEAEYYC**ALWYSNLWV**FGGGTKLTVL

Nucleic acid sequence
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTCCTGG

CGGCACAGTGACCCTGACCTGTAGATCTTCTACAG

GCGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGgAGAAG

CCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAAC

AAACAAGAGAGCCCCTTGGACACCCGCCAGATTCTCTGGATCTC

TGCTCGGCGGAAAGGCCGCTCTGACACTTTCTGGT

GCTCAGCCTGAGGACGAGGCCGAGTACTATTGTGCCCTGTGGTA

CAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAAC

TGACAGTTCTG

[0227] The amino acid sequence of hVL3 is shown in SEQ ID NO. 12, its encoding nucleic acid is shown in SEQ ID NO. 13, and its LCDR1, LCDR2 and LCDR3 are shown in SEQ ID NOs. 14, 15 and 9, respectively.

EAVVTQEPSLTVSPGGTVTLTC**ESSDGAVTTSNYAN**WVQE

KPGQAPRGLIG**GTNKEAP**WTPARFSGSLLGGKAALTLSGA

QPEDEAEYYC**ALWYSNLWV**FGGGTKLTVL

Nucleic acid sequence
GAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTC

CTGGCGGCACAGTGACCCTGACCTGTGAGTCTTCTGACGG

CGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGGAG

AAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAA

ACAAGGAGGCCCCTTGGACACCCGCCAGATTCTCTGGATC

TCTGCTCGGCGGAAAGGCCGCTCTGACACTTTCTGGTGCT

CAGCCTGAGGACGAGGCCGAGTACTATTGTGCCCTGTGGT

ACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAACTGAC

AGTTCTG

[0228] The amino acid sequence of hVL4 is shown in SEQ ID NO. 16, nucleic acid encoding the same is shown in SEQ ID NO. 17, and LCDR1, LCDR2 and LCDR3 thereof are shown in SEQ ID NOs. 14, 15 and 9, respectively.

QAVVTQEPSLTVSPGGTVTLTC**ESSDGAVTTSNYAN**WVQE

KPGQAPRGLIG**GTNKEA**PWTPARFSGSLLGGKAALTLSGA

QPEDEAEYYC**ALWYSNLWV**FGGGTKLTVL

Nucleic acid sequence
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTC

CTGGCGGCACAGTGACCCTGACCTGTGAGTCTTCTGACGG

CGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGGAG

AAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAA

ACAAGGAGGCCCCTTGGACACCCGCCAGATTCTCTGGATC

TCTGCTCGGCGGAAAGGCCGCTCTGACACTTTCTGGTGCT

CAGCCTGAGGACGAGGCCGAGTACTATTGTGCCCTGTGGT

ACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAACTGAC

AGTTCTG

[0229] The amino acid sequence of hVL5 is shown in SEQ ID NO. 18, nucleic acid encoding the same is shown in SEQ ID NO. 19, and LCDR1, LCDR2 and LCDR3 thereof are shown in SEQ ID NOs. 7, 8 and 21, respectively.

QAVVTQEPSLTVSPGGTVTLTC**RSSTGAVTTSNYAN**WVQE

KPGQAPRGLIG**GTNKRAP**WTPARFSGSLLGGKAALTITGA

QAEDEAEYYC**VLWYSNLWV**FGGGTKLTVL

Nucleic acid sequence
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTC

CTGGCGGCACAGTGACCCTGACCTGTAGATCTTCTACAGG

CGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGgAG

AAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAA

ACAAGAGAGCCCCTTGGACACCCGCCAGATTCTCTGGATC

TCTGCTCGGCGGAAAGGCCGCTCTGACAATCACTGGTGCT

CAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGT

ACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAACTGAC

AGTTCTG

[0230] The amino acid sequence of hVL6 is shown in SEQ ID NO. 22, nucleic acid encoding the same is shown in SEQ ID NO. 23, and LCDR1, LCDR2 and LCDR3 thereof are shown in SEQ ID NOs. 7, 20 and 21, respectively.

QAVVTQEPSLTVSPGGTVTLTC**RSSTGAVTTSNYAN**WFQE

KPGQAPRGLIY**GTNKRAP**WTPARFSGSLLGGKAALTLSGA

QAEDEAEYYC**VLWYSNLWV**FGGGTKLTVL

Nucleic acid sequence
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTC

CTGGCGGCACAGTGACCCTGACCTGTAGATCTTCTACAGG

CGCCGTGACCACCAGCAACTACGCTAATTGGTTCCAGGAG

-continued

AAGCCCGGCCAGGCTCCTAGAGGACTGATCTACGGAACAA

ACAAGAGAGCCCCTTGGACACCCGCCAGATTCTCTGGATC

TCTGCTCGGCGGAAAGGCCGCTCTGACACTTTCTGGTGCT

CAGGCTGAGGACGAGGCCGAGTACTATTGTGTCCTGTGGT

ACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAACTGAC

AGTTCTG

[0231] The amino acid sequence of hVH1 is shown in SEQ ID NO. 24, nucleic acid encoding the same is shown in SEQ ID NO. 25, and HCDR1, HCDR2 and HCDR3 thereof are shown in SEQ ID NOs. 26, 27 and 28, respectively.

EVQLVESGGGLVQPGGSLRLSCAASGFTF**NTYAMN**WVRQA

PGKGLEWVSR**IRSKYNNYATYYADSVKD**RFTISRDDSKNT

LYLQMNSLRAEDTAVYYCVR**HGNFGNSYVSWFAY**WGQGTL

VTVSS

Nucleic acid sequence
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC

CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT

CACCTTCAACACCTACGCTATGAACTGGGTCCGACAGGCC

CCTGGCAAAGGACTGGAATGGGTGTCCAGAATCAGGTCCA

AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA

GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACACC

CTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCG

CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG

CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG

GTCACAGTTAGCTCT

[0232] The amino acid sequence of hVH2 is shown in SEQ ID NO. 29, nucleic acid encoding the same is shown in SEQ ID NO. 30, and HCDR1, HCDR2 and HCDR3 thereof are shown in SEQ ID NOs. 31, 27 and 28, respectively.

EVQLVESGGGLVQPGGSLRLSCAASGFTF**STYAMN**WVRKA

PGKGLEWVSR**IRSKYNNYATYYADSVKD**RFTISRDDSKNT

LYLQMNSLRAEDTAVYYCVR**HGNFGNSYVSWFAY**WGQGTL

VTVSS

Nucleic acid sequence
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC

CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT

CACCTTCtcCACCTACGCTATGAACTGGGTCCGAaagGCC

CCTGGCAAAGGACTGGAATGGGTGTCCAGAATCAGGTCCA

AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA

GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACACC

CTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCG

-continued

CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG

CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG

GTCACAGTTAGCTCT

[0233] The amino acid sequence of hVH3 is shown in SEQ ID NO. 32, nucleic acid encoding the same is shown in SEQ ID NO. 33, and HCDR1, HCDR2 and HCDR3 thereof are shown in SEQ ID NOs. 31, 27 and 34, respectively.

EVQLVESGGGLVQPGGSLRLSCAASGFTF**STYAMN**WVRKA

PGKGLEWVSR**IRSKYNNYATYYADSVKD**RFTISRDDSKNT

LYLQMNSLRAEDTAVYYCVR**HGNFGESYVSWFAY**WGQGTL

VTVSS

Nucleic acid sequence
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC

CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT

CACCTTCTCCACCTACGCTATGAACTGGGTCCGAAAGGCC

CCTGGCAAAGGACTGGAATGGGTGTCCAGAATCAGGTCCA

AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA

GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACACC

CTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCG

CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCGAGAG

CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG

GTCACAGTTAGCTCT

[0234] The amino acid sequence of hVH4 is shown in SEQ ID NO. 35, nucleic acid encoding the same is shown in SEQ ID NO. 36, and HCDR1, HCDR2 and HCDR3 thereof are shown in SEQ ID NOs. 31, 27 and 37, respectively.

EVQLVESGGGLVQPGGSLRLSCAASGFTF**STYAMN**WVRKA

PGKGLEWVSR**IRSKYNNYATYYADSVKD**RFTISRDDSKNT

LYLQMNSLRAEDTAVYYCVR**HGNFGQSYVSWFAY**WGQGTL

VTVSS

Nucleic acid sequence
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC

CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT

CACCTTCTCCACCTACGCTATGAACTGGGTCCGAAAGGCC

CCTGGCAAAGGACTGGAATGGGTGTCCAGAATCAGGTCCA

AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA

GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACACC

CTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCG

CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCCAGAG

-continued

CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG

GTCACAGTTAGCTCT

[0235] The amino acid sequence of hVH5 is shown in SEQ ID NO. 38, nucleic acid encoding the same is shown in SEQ ID NO. 39, and HCDR1, HCDR2 and HCDR3 thereof are shown in SEQ ID NOs. 31, 27 and 40, respectively.

EVQLVESGGGLVQPGGSLRLSCAASGFTF**STYAMN**WVRKA

PGKGLEWVSR**IRSKYNNYATYYADSVKD**RFTISRDDSKNT

LYLQMNSLRAEDTAVYYCVR**HGNFGDSYVSWFAY**WGQGTL

VTVSS

Nucleic acid sequence
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC

CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT

CACCTTCTCCACCTACGCTATGAACTGGGTCCGAAAGGCC

CCTGGCAAAGGACTGGAATGGGTGTCCAGAATCAGGTCCA

AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA

GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACACC

CTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCG

CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCGACAG

CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG

GTCACAGTTAGCTCT

[0236] The amino acid sequence of hVH6 is shown in SEQ ID NO. 41, nucleic acid encoding the same is shown in SEQ ID NO. 42, and HCDR1, HCDR2 and HCDR3 thereof are shown in SEQ ID NOs. 31, 27 and 43, respectively.

EVQLVESGGGLVQPGGSLRLSCAASGFTF**STYAMN**WVRKA

PGKGLEWVSR**IRSKYNNYATYYADSVKD**RFTISRDDSKNT

LYLQMNSLRAEDTAVYYCVR**HGNFGTSYVSWFAY**WGQGTL

VTVSS

Nucleic acid sequence
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC

CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT

CACCTTCTCCACCTACGCTATGAACTGGGTCCGAAAGGCC

CCTGGCAAAGGACTGGAATGGGTGTCCAGAATCAGGTCCA

AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA

GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACACC

CTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCG

CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCACCAG

CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG

GTCACAGTTAGCTCT

[0237] The amino acid sequence of hVH7 is shown in SEQ ID NO. 44, nucleic acid encoding the same is shown in SEQ ID NO. 45, and HCDR1, HCDR2 and HCDR3 thereof are shown in SEQ ID NOs. 46, 47 and 28, respectively.

EVQLVESGGGLVQPGGSLRLSCAASGFTF**SDYAMN**WVRKA

PGKGLEWVSR**IRSKYNNYATYYADSVED**RFTISRDDSKNT

LYLQMNSLRAEDTAVYYCVR**HGNFGNSYVSWFAY**WGQGTL

VTVSS

Nucleic acid sequence
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC

CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT

CACCTTCTCCGACTACGCTATGAACTGGGTCCGAAAGGCC

CCTGGCAAAGGACTGGAATGGGTGTCCAGAATCAGGTCCA

AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGGA

GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACACC

CTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCG

CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG

CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG

GTCACAGTTAGCTCT

[0238] The amino acid sequence of hVH8 is shown in SEQ ID NO. 48, nucleic acid encoding the same is shown in SEQ ID NO. 49, and HCDR1, HCDR2 and HCDR3 thereof are shown in SEQ ID NOs. 26, 27 and 28, respectively.

EVQLVESGGGLVQPGGSLRLSCAASGFTF**NTYAMN**WVRKA

PGKGLEWVGR**IRSKYNNYATYYADSVKD**RFTISRDDSKNS

LYLQMNSLKTEDTAVYYCAR**HGNFGNSYVSWFAY**WGQGTL

VTVSS

Nucleic acid sequence
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC

CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT

CACCTTCAACACCTACGCTATGAACTGGGTCCGAAAGGCC

CCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCA

AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA

GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACAGC

CTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCG

CCGTGTACTACTGTGCCAGACACGGCAACTTCGGCAACAG

CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG

GTCACAGTTAGCTCT

[0239] The amino acid sequence of hVH9 is shown in SEQ ID NO. 50, nucleic acid encoding the same is shown in SEQ ID NO. 51, and HCDR1, HCDR2 and HCDR3 thereof are shown in SEQ ID NOs. 26, 27 and 28, respectively.

EVQLVESGGGLVQPGGSLRLSCAASGFTF**NTYAMN**WVRKA

PGKGLEWVGR**IRSKYNNYATYYADSVKD**RFTISRDDSKNS

LYLQMNSLKTEDTAVYYCVR**HGNFGNSYVSWFAY**WGQGTL

VTVSS

Nucleic acid sequence
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC

CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT

CACCTTCAACACCTACGCTATGAACTGGGTCCGAAAGGCC

CCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCA

AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA

GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACAGC

CTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCG

CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG

CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG

GTCACAGTTAGCTCT

[0240] The amino acid sequence of hVH10 is shown in SEQ ID NO. 52, nucleic acid encoding the same is shown in SEQ ID NO. 53, and HCDR1, HCDR2 and HCDR3 thereof are shown in SEQ ID NOs. 26, 27 and 28, respectively.

EVQLVESGGGLVQPGGSLRLSCAASGFTF**NTYAMN**WVRKA

PGKGLEWVAR**IRSKYNNYATYYADSVKD**RFTISRDDSKNS

LYLQMNSLKTEDTAVYYCVR**HGNFGNSYVSWFA**YWGQGTL

VTVSS

Nucleic acid sequence
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC

CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT

CACCTTCAACACCTACGCTATGAACTGGGTCCGAAAGGCC

CCTGGCAAAGGACTGGAATGGGTGGCCAGAATCAGGTCCA

AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA

GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACAGC

CTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCG

CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG

CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG

GTCACAGTTAGCTCT

[0241] After the humanized variants of light and heavy chain have been respectively subjected to full sequence synthesis, they are cloned into the eukaryotic expression vector containing the constant region of light chain of antibody λ or the constant region CH1-CH3 of heavy chain of human IgG4, co-transfected into HEK 293E cells, and cultured at 37° C. under 120 rpm of 5% CO_2 for 5-6 days, and then the culture supernatant is collected and purified by Protein A chromatography column.

3. Affinity of Humanized CD3 Antibody

[0242] Human CD3εγ recombinant protein was coated overnight at 4° C. After blocking with 2% skim milk, different dilutions of CD3 antibody were added to each well and incubated for 1 hour. After the secondary antibody was developed by adding HPR-labeled goat anti-human IgG Fc and TMB solution, the reaction was stopped with concentrated sulfuric acid and the absorbance was read at 450 nm. FIG. **2** shows the binding of humanized anti-CD3 antibodies (including aCD3-hVH1/VL5, aCD3-hVH8/VL1, aCD3-hVH8/VL5, aCD3-hVH9/VL1, aCD3-hVH9/VL2, aCD3-hVH9/VL3, aCD3-hVH9/VL5) to human CD3εγ protein, where humanized CD3 antibodies bind with high affinity to CD3εγ recombinant protein.

[0243] Jurkat cells in logarithmic growth phase were blocked with 3% BSA for 30 min, added to 96-well U-plate at 5×104 cells per well, centrifuged to discard the supernatant, and added with 50 μL of gradient diluted antibody (antibody concentration: from 30 μg/mL, with 3-fold dilution for 5 gradients) per well, and incubated at 4° C. for 1 hour. After washing off the primary antibody, a 1: 300 dilution of Alexa Fluro647 labeled goat anti-human IgG Fc (Jackson ImmunoResearch, 109-606-170) was added to the secondary antibody, incubated for 45 min at 4° C., and, after washing, resuspended in 50 μL of PBS per well for FACS (iQue, intellicyt) detection. As a result, as shown in FIG. **3**, the humanized anti-CD3 antibody bound to Jurkat cells, wherein both humanized anti-CD3 antibodies hVH9/VL5 (aCD3-hVH9/VL5) and hVH9/VL2 (aCD3-hVH9/VL2) were significantly weaker than the control antibody OKT3, and bound to Jurkat cells with moderate affinity.

[0244] Table 2 shows the affinity of the humanized CD3 antibody to CD3 recombinant protein and Jurkat cells.

TABLE 2

Affinities of humanized anti-CD3 antibodies

	ELISA (CD3εγ)	FACS (Jurkat)
aCD3-hVH1/VL5	0.60 nM	10 nM
aCD3-hVH8/VL1	0.65 nM	15 nM
aCD3-hVH8/VL5	0.74 nM	Weak
aCD3-hVH9/VL1	0.49 nM	7 nM
aCD3-hVH9/VL2	0.44 nM	25 nM
aCD3-hVH9/VL3	0.70 nM	Weak
aCD3-hVH9/VL5	0.42 nM	20 nM
OKT3-hIgG1	ND	0.27 nM
KLH-hIgG4	—	—

ND: not detected.
—: not combined with

4. Cross-Recognition of Humanized Anti-CD3 Antibody with Human and Cynomolgus Monkey CD3 Antigens

[0245] Human CD3εγ protein and cynomolgus monkey CD3εγ protein were coated separately overnight at 4° C. After blocking with 2% skim milk, different dilutions of CD3 antibody were added to each well and incubated for 1 hour. After the secondary antibody was developed by adding HPR-labeled goat anti-human IgG Fc and TMB solution, the reaction was stopped with concentrated sulfuric acid, and the absorbance was read at 450 nm. FIG. **4** shows that both humanized anti-CD3 antibodies hVH9/VL5 (aCD3-hVH9/VL5) and hVH9/VL2 (aCD3-hVH9/VL2) can bind both human CD3εγ and cynomolgus monkey CD3εγ proteins.

Example 2: Construction of Anti-CD20×CD3 κλ Bispecific Antibodies Formed by Different Types of Light Chains

1. Construction of Anti-CD20×CD3 κλ Bispecific Antibody

[0246] A novel T-cell κλ bispecific antibody with the native IgG configuration was constructed with the humanized CD3 antibody hVH9/VL5 (λ light chain and paired heavy chain) and the humanized CD20 antibody (κ light chain and paired heavy chain).

[0247] As shown in FIG. **5**, the following five CD20×CD3 bispecific antibodies were designed and constructed:

[0248] 1) CD20×CD3 κλ001: retaining the native sequences of the CD3 arm and the CD20 antigen arm;

[0249] 2) CD20×CD3 κλ002: a charge variant ($V\kappa_{CD20}$: $Gln_{38}Lys$; VH_{CD20}: $Gln_{39}Glu$; $V\lambda_{CD3}$: $Gln_{40}Glu$; VH_{CD3}: $Gln_{39}Lys$);

[0250] 3) CD20×CD3 κλ003: based on CD20×CD3 κλ002, adding between CH1/CκS complementary charge pairs ($V\kappa$-Ck_{CD20}: $Gln_{38}Lys$\$Glu_{123}Lys$\$Gln_{124}Lys$; V_H-C_H1_{CD20}: $Gln_{39}Glu$\$Lys_{152}Glu$\$Lys_{218}Glu$; $V\kappa_{CD3}$: $Gln_{40}Glu$; VH_{CD3}: $Gln_{39}Lys$);

[0251] 4) CD20×CD3 κλ004: introducing, only in the CD20 antigen arm, charge variants ($V\lambda_{CD20}$: $Gln_{38}Lys$; VH_{CD20}: $Gln_{39}Glu$);

[0252] 5) CD20×CD3 κλ005: introducing, only in the CD3 arm, charge variants ($V\lambda_{CD3}$: $Gln_{40}Glu$; VH_{CD3}: $Gln_{39}Lys$).

[0253] The corresponding sequences are shown in Table 3. The control antibody CD20×CD3-crossFab was constructed by reference to the CrossFab method (Schaefer W et al. PNAS 2011).

TABLE 3

Sequences of anti-CD20×CD3 κλ bispecific antibodies

	light chain of CD20 arm	heavy chain of CD20 arm	light chain of CD3 arm	heavy chain of CD3 arm
CD20×CD3 κλ001	SEQ ID NO. 54	SEQ ID NO.56	SEQ ID NO. 58	SEQ ID NO. 60
CD20×CD3 κλ002	SEQ ID NO. 62	SEQ ID NO.64	SEQ ID NO. 66	SEQ ID NO. 68
CD20×CD3 κλ003	SEQ ID NO. 70	SEQ ID NO.72	SEQ ID NO. 66	SEQ ID NO. 68
CD20×CD3 κλ004	SEQ ID NO. 62	SEQ ID NO.64	SEQ ID NO. 58	SEQ ID NO. 60
CD20×CD3 κλ005	SEQ ID NO. 54	SEQ ID NO.56	SEQ ID NO. 66	SEQ ID NO. 68
CD20×CD3-crossFab	SEQ ID NO. 70	SEQ ID NO.74	SEQ ID NO. 76	SEQ ID NO. 78

CD20×CD3 κλ001:
κ light chain of CD20 arm: SEQ ID NO. 54
EIVLTQSPGTLSLSPGERATLSCRASQSVSSYLAWYQQKP
GQAPRLLIYDASNRATGIPDRFSGSGSGTDFTLTISRLEP
EDFAVYYCQQRSNWPITFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

TABLE 3-continued

Sequences of anti-CD20×CD3 κλ bispecific antibodies

Nucleotide sequence:
SEQ ID NO. 55
GAGATCGTGCTGACACAGAGCCCTGGCACACTGTCACTGT
CTCCAGGCGAGAGAGCCACACTGAGCTGTAGAGCCAGCCA
GAGCGTGTCCTCTTACCTGGCCTGGTATCAGCAGAAGCCT
GGACAGGCTCCCAGACTGCTGATCTACGACGCCAGCAACA
GAGCCACAGGCATCCCCGATAGATTCAGCGGCTCTGGCTC
TGGCACCGACTTCACCCTGACAATCAGCAGACTGGAACCC
GAGGACTTCGCCGTGTACTACTGCCAGCAGAGAAGCAACT
GGCCCATCACATTCGGCCAGGGCACCAAGCTGGAAATCAA
GCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCA
TCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACA
GCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GT

Heavy chain (heavy chain 1) of CD20 arm:
SEQ ID NO. 56
EVQLLESGGGVVQPGGSLRLSCAASGFTFNDYAMHWVRQA
PGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNSKNTLY
LQMNSLRAEDTAVYYCAKDIQYGNYYYGMDYWGQGTLVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEM
TKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK

Nucleotide sequence:
SEQ ID NO. 57
GAAGTGCAGCTGCTGGAATCTGGTGGCGGAGTTGTTCAGC
CTGGCGGCTCTCTGAGACTGTCTTGTGCTGCCAGCGGCTT
CACCTTCAACGACTACGCTATGCACTGGGTCCGACAGGCC
CCTGGCAAAGGACTTGAATGGGTGTCCACCATCAGCTGGA
ACAGCGGCTCTATCGGCTACGCCGATTCCGTGAAGGGCAG
ATTCACCATCTCCAGAGACAACAGCAAGAACACCCTGTAC
CTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGT
ACTACTGTGCCAAGGACATCCAGTACGGCAACTACTACTA
CGGCATGGACTACTGGGGCCAGGGAACACTGGTTACCGTT
AGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGG
CCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCT
GGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC
GTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCATA
CCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCT
GAGCAGCGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACC
AAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACA
CCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTCC
CTGCCCCCCTTGCCCTGCCCCCGAGTTCGAGGGCGGACCT
AGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGA
TGATCAGCAGAACCCCCGAGGTGACCTGCGTGGTGGTGGA
CGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTAC
GTGGACGGCGTGGAAGTGCATAACGCCAAGACCAAGCCCA
GAGAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGT
GCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAA
TACAAGTGCAAGGTCTCCAACAAGGGCCTGGCCAGCAGCA
TCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGA
GCCCCAGGTCTGCACCCTGCCACCTAGCCAAGAGGAGATG
ACCAAGAACCAGGTGTCCCTGAGCTGTGCCGTGAAAGGCT
TCTATCCCAGCGATATCGCCGTGGAGTGGGAGAGCAACGG
CCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTG
GACAGCGACGGCAGCTTCTTCCTGGTTTCCAAGCTGACCG
TGGACAAGTCCAGATGGCAGGAGGGCAACGTCTTCAGCTG

TABLE 3-continued

Sequences of anti-CD20×CD3 κλ bispecific antibodies

CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAG
AAGTCCCTGAGCCTGAGCCTGGGCAAG

λ light chain of CD3 arm
SEQ ID NO. 58
QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQ
KPGQAPRGLIGGTNKRAPWTPARFSGSLLGGKAALTITGA
QAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVTL
FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH
EGSTVEKTVAPTECS

Nucleotide sequence: SEQ ID NO. 59
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTC
CTGGCGGCACAGTGACCCTGACCTGTAGATCTTCTACAGG
CGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGCAG
AAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAA
ACAAGAGAGCCCCTTGGACACCCGCCAGATTCTCTGGATC
TCTGCTCGGCGGAAAGGCCGCTCTGACAATCACTGGTGCT
CAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGT
ACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAACTGAC
AGTTCTGGGTCAGCCCAAGGCGGCGCCCTCGGTCACTCTG
TTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCA
CACTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGT
GACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCG
GGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACA
AGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCA
GTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCAT
GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAAT
GTTCA

Heavy chain (heavy chain 2) of CD3 arm:
SEQ ID NO. 60
EVOLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQA
PGKGLEWVGRIRSKYNNYATYYADSVKDRFTISRDDSKNS
LYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQGTL
VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFE
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF
NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQ
EEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 61
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC
CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT
CACCTTCAACACCTACGCTATGAACTGGGTCCGACAGGCC
CCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCA
AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA
GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACAGC
CTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCG
CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG
CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG
GTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGT
TCCCCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCAC
AGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG
CCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCG
GCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACT
GTACTCCCTGAGCAGCGTGGTGACCGTGCCTTCCAGCAGC
CTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGC
CCAGCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTA
CGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCGAG
GGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGG
ACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGT
GGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTT
AATTGGTACGTGGACGGCGTGGAAGTGCATAACGCCAAGA
CCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAGAGT
GGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAAC
GGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGGCCTGG
CCAGCAGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCA
GCCACGGGAGCCCCAGGTCTACACCCTGCCACCTTGTCAA
GAGGAGATGACCAAGAACCAGGTGTCCCTGTGGTGTCTGG
TGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGGGA
GAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCC
CCTGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCA
AGCTGACCGTGGACAAGTCCAGATGGCAGGAGGGCAACGT
CTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCAC
TACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

CD2 0×CD3 κλ002:
κ light chain of CD20 arm: SEQ ID NO. 62
EIVLTQSPGTLSLSPGERATLSCRASQSVSSYLAWYQKKP
GQAPRLLIYDASNRATGIPDRFSGSGSGTDFTLTISRLEP
EDFAVYYCQQRSNWPITFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

Nucleotide sequence: SEQ ID NO. 63
GAGATCGTGCTGACACAGAGCCCTGGCACACTGTCACTGT
CTCCAGGCGAGAGAGCCACACTGAGCTGTAGAGCCAGCCA
GAGCGTGTCCTCTTACCTGGCCTGGTATCAGAAGAAGCCT
GGACAGGCTCCCAGACTGCTGATCTACGACGCCAGCAACA
GAGCCACAGGCATCCCCGATAGATTCAGCGGCTCTGGCTC
TGGCACCGACTTCACCCTGACAATCAGCAGACTGGAACCC
GAGGACTTCGCCGTGTACTACTGCCAGCAGAGAAGCAACT
GGCCCATCACATTCGGCCAGGGCACCAAGCTGGAAATCAA
GCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCA
TCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACA
GCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GT

Heavy chain (heavy chain 1) of CD20 arm:
SEQ ID NO. 64
EVQLLESGGGVVQPGGSLRLSCAASGFTFNDYAMHWVREA
PGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNSKNTLY
LQMNSLRAEDTAVYYCAKDIQYGNYYYGMDYWGQGTLVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEM
TKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK

Nucleotide sequence: SEQ ID NO. 65
GAAGTGCAGCTGCTGGAATCTGGTGGCGGAGTTGTTCAGC
CTGGCGGCTCTCTGAGACTGTCTTGTGCTGCCAGCGGCTT
CACCTTCAACGACTACGCTATGCACTGGGTCCGAGAGGCC
CCTGGCAAAGGACTTGAATGGGTGTCCACCATCAGCTGGA
ACAGCGGCTCTATCGGCTACGCCGATTCCGTGAAGGGCAG
ATTCACCATCTCCAGAGACAACAGCAAGAACACCCTGTAC
CTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGT
ACTACTGTGCCAAGGACATCCAGTACGGCAACTACTACTA
CGGCATGGACTACTGGGGCCAGGGAACACTGGTTACCGTT
AGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGG
CCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCT
GGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC
GTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCATA
CCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCT
GAGCAGCGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACC
AAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACA
CCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTCC
CTGCCCCCCTTGCCCTGCCCCCGAGTTCGAGGGCGGACCT
AGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGA
TGATCAGCAGAACCCCCGAGGTGACCTGCGTGGTGGTGGA
CGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTAC
GTGGACGGCGTGGAAGTGCATAACGCCAAGACCAAGCCCA

TABLE 3-continued

Sequences of anti-CD20×CD3 κλ bispecific antibodies

GAGAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGT
GCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAA
TACAAGTGCAAGGTCTCCAACAAGGGCCTGGCCAGCAGCA
TCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGA
GCCCCAGGTCTGCACCCTGCCACCTAGCCAAGAGGAGATG
ACCAAGAACCAGGTGTCCCTGAGCTGTGCCGTGAAAGGCT
TCTATCCCAGCGATATCGCCGTGGAGTGGGAGAGCAACGG
CCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTG
GACAGCGACGGCAGCTTCTTCCTGGTTTCCAAGCTGACCG
TGGACAAGTCCAGATGGCAGGAGGGCAACGTCTTCAGCTG
CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAG
AAG
TCCCTGAGCCTGAGCCTGGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 66
QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQE
KPGQAPRGLIGGTNKRAPWTPARFSGSLLGGKAALTITGA
QAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVTL
FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH
EGSTVEKTVAPTECS

Nucleotide sequence: SEQ ID NO. 67
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTC
CTGGCGGCACAGTGACCCTGACCTGTAGATCTTCTACAGG
CGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGGAG
AAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAA
ACAAGAGAGCCCCTTGGACACCCGCCAGATTCTCTGGATC
TCTGCTCGGCGGAAAGGCCGCTCTGACAATCACTGGTGCT
CAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGT
ACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAACTGAC
AGTTCTGGGTCAGCCCAAGGCGGCGCCCTCGGTCACTCTG
TTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCA
CACTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGT
GACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCG
GGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACA
AGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCA
GTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCAT
GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAAT
GTTCA

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 68
EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRKA
PGKGLEWVGRIRSKYNNYATYYADSVKDRFTISRDDSKNS
LYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQGTL
VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFE
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF
NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQ
EEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 69
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC
CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT
CACCTTCAACACCTACGCTATGAACTGGGTCCGAAAGGCC
CCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCA
AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA
GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACAGC
CTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCG
CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG
CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG
GTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGT
TCCCCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCAC
AGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG
CCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCG
GCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACT
GTACTCCCTGAGCAGCGTGGTGACCGTGCCTTCCAGCAGC
CTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGC
CCAGCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTA
CGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCGAG
GGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGG
ACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGT
GGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTT
AATTGGTACGTGGACGGCGTGGAAGTGCATAACGCCAAGA
CCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAGAGT
GGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAAC
GGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGGCCTGG
CCAGCAGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCA
GCCACGGGAGCCCCAGGTCTACACCCTGCCCACCTTGTCAA
GAGGAGATGACCAAGAACCAGGTGTCCCTGTGGTGTCTGG
TGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGGGA
GAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCC
CCTGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCA
AGCTGACCGTGGACAAGTCCAGATGGCAGGAGGGCAACGT
CTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCAC
TACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

CD2 0×CD3 κλ003:
κ light chain of CD20 arm: SEQ ID NO. 70
EIVLTQSPGTLSLSPGERATLSCRASQSVSSYLAWYQKKP
GQAPRLLIYDASNRATGIPDRFSGSGSGTDFTLTISRLEP
EDFAVYYCQQRSNWPITFGQGTKLEIKRTVAAPSVFIFPP
SDKKLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

Nucleotide sequence: SEQ ID NO. 71
GAGATCGTGCTGACACAGAGCCCTGGCACACTGTCACTGT
CTCCAGGCGAGAGAGCCACACTGAGCTGTAGAGCCAGCCA
GAGCGTGTCCTCTTACCTGGCCTGGTATCAGAAGAAGCCT
GGACAGGCTCCCAGACTGCTGATCTACGACGCCAGCAACA
GAGCCACAGGCATCCCCGATAGATTCAGCGGCTCTGGCTC
TGGCACCGACTTCACCCTGACAATCAGCAGACTGGAACCC
GAGGACTTCGCCGTGTACTACTGCCAGCAGAGAAGCAACT
GGCCCATCACATTCGGCCAGGGCACCAAGCTGGAAATCAA
GCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCA
TCTGATAAGAAATTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACA
GCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GT

Heavy chain (heavy chain 1) of CD20 arm: SEQ ID NO. 72
EVQLLESGGGVVQPGGSLRLSCAASGFTFNDYAMHWVREA
PGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNSKNTLY
LQMNSLRAEDTAVYYCAKDIQYGNYYYGMDYWGQGTLVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVEDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDERVESKYGPPCPPCPAPEFEGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEM
TKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK

Nucleotide sequence: SEQ ID NO. 73
GAAGTGCAGCTGCTGGAATCTGGTGGCGGAGTTGTTCAGC
CTGGCGGCTCTCTGAGACTGTCTTGTGCTGCCAGCGGCTT
CACCTTCAACGACTACGCTATGCACTGGGTCCGAGAGGCC
CCTGGCAAAGGACTTGAATGGGTGTCCACCATCAGCTGGA
ACAGCGGCTCTATCGGCTACGCCGATTCCGTGAAGGGCAG
ATTCACCATCTCCAGAGACAACAGCAAGAACACCCTGTAC
CTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGT
ACTACTGTGCCAAGGACATCCAGTACGGCAACTACTACTA
CGGCATGGACTACTGGGGCCAGGGAACACTGGTTACCGTT
AGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGG
CCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCT
GGGCTGCCTGGTGGAGGACTACTTCCCCGAGCCCGTGACC

TABLE 3-continued

Sequences of anti-CD20×CD3 κλ bispecific antibodies

GTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCATA
CCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCT
GAGCAGCGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACC
AAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACA
CCAAGGTGGACGAGAGAGTGGAGAGCAAGTACGGCCCTCC
CTGCCCCCCTTGCCCTGCCCCCGAGTTCGAAGGCGGACCT
AGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGA
TGATCAGCAGAACCCCCGAGGTGACCTGCGTGGTGGTGGA
CGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTAC
GTGGACGGCGTGGAAGTGCATAACGCCAAGACCAAGCCCA
GAGAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGT
GCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAA
TACAAGTGCAAGGTCTCCAACAAGGGCCTGGCCAGCAGCA
TCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGA
GCCCCAGGTCTGCACCCTGCCCACCTAGCCAAGAGGAGATG
ACCAAGAACCAGGTGTCCCTGAGCTGTGCCGTGAAAGGCT
TCTATCCCAGCGATATCGCCGTGGAGTGGGAGAGCAACGG
CCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTG
GACAGCGACGGCAGCTTCTTCCTGGTTTCCAAGCTGACCG
TGGACAAGTCCAGATGGCAGGAGGGCAACGTCTTCAGCTG
CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAG
AAGTCCCTGAGCCTGAGCCTGGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 66
QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQE
KPGQAPRGLIGGTNKRAPWTPARFSGSLLGGKAALTITGA
QAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVTL
FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH
EGSTVEKTVAPTECS

Nucleotide sequence: SEQ ID NO. 67
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTC
CTGGCGGCACAGTGACCCTGACCTGTAGATCTTCTACAGG
CGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGGAG
AAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAA
ACAAGAGAGCCCCTTGGACACCCGCCAGATTCTCTGGATC
TCTGCTCGGCGGAAAGGCCGCTCTGACAATCACTGGTGCT
CAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGT
ACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAACTGAC
AGTTCTGGGTCAGCCCAAGGCGGCGCCCTCGGTCACTCTG
TTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCA
CACTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGT
GACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCG
GGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACA
AGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCA
GTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCAT
GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAAT
GTTCA

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 68
EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRKA
PGKGLEWVGRIRSKYNNYATYYADSVKDRFTISRDDSKNS
LYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQGTL
VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFE
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF
NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQ
EEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 69
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC
CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT
CACCTTCAACACCTACGCTATGAACTGGGTCCGAAAGGCC
CCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCA
AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA
GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACAGC
CTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCG
CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG
CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG
GTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGT
TCCCCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCAC
AGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG
CCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCG
GCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACT
GTACTCCCTGAGCAGCGTGGTGACCGTGCCTTCCAGCAGC
CTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGC
CCAGCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTA
CGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCGAG
GGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGG
ACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGT
GGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTT
AATTGGTACGTGGACGGCGTGGAAGTGCATAACGCCAAGA
CCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAGAGT
GGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAAC
GGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGGCCTGG
CCAGCAGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCA
GCCACGGGAGCCCCAGGTCTACACCCTGCCACCTTGTCAA
GAGGAGATGACCAAGAACCAGGTGTCCCTGTGGTGTCTGG
TGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGGGA
GAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCC
CCTGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCA
AGCTGACCGTGGACAAGTCCAGATGGCAGGAGGGCAACGT
CTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCAC
TACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

CD2 0×CD3 κλ004:
κ light chain of CD20 arm: SEQ ID NO. 62
EIVLTQSPGTLSLSPGERATLSCRASQSVSSYLAWYQKKP
GQAPRLLIYDASNRATGIPDRFSGSGSGTDFTLTISRLEP
EDFAVYYCQQRSNWPITFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

Nucleotide sequence: SEQ ID NO. 63
GAGATCGTGCTGACACAGAGCCCTGGCACACTGTCACTGT
CTCCAGGCGAGAGAGCCACACTGAGCTGTAGAGCCAGCCA
GAGCGTGTCCTCTTACCTGGCCTGGTATCAGAAGAAGCCT
GGACAGGCTCCCAGACTGCTGATCTACGACGCCAGCAACA
GAGCCACAGGCATCCCCGATAGATTCAGCGGCTCTGGCTC
TGGCACCGACTTCACCCTGACAATCAGCAGACTGGAACCC
GAGGACTTCGCCGTGTACTACTGCCAGCAGAGAAGCAACT
GGCCCATCACATTCGGCCAGGGCACCAAGCTGGAAATCAA
GCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCA
TCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACA
GCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GT

Heavy chain (heavy chain 1) of CD20 arm: SEQ ID NO. 64
EVQLLESGGGVVQPGGSLRLSCAASGFTFNDYAMHWVREA
PGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNSKNTLY
LQMNSLRAEDTAVYYCAKDIQYGNYYYGMDYWGQGTLVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEM
TKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK

Nucleotide sequence: SEQ ID NO. 65
GAAGTGCAGCTGCTGGAATCTGGTGGCGGAGTTGTTCAGC
CTGGCGGCTCTCTGAGACTGTCTTGTGCTGCCAGCGGCTT
CACCTTCAACGACTACGCTATGCACTGGGTCCGAGAGGCC

TABLE 3-continued

Sequences of anti-CD20×CD3 κλ bispecific antibodies

CCTGGCAAAGGACTTGAATGGGTGTCCACCATCAGCTGGA
ACAGCGGCTCTATCGGCTACGCCGATTCCGTGAAGGGCAG
ATTCACCATCTCCAGAGACAACAGCAAGAACACCCTGTAC
CTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGT
ACTACTGTGCCAAGGACATCCAGTACGGCAACTACTACTA
CGGCATGGACTACTGGGGCCAGGGAACACTGGTTACCGTT
AGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGG
CCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCT
GGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC
GTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCATA
CCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCT
GAGCAGCGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACC
AAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACA
CCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTCC
CTGCCCCCCTTGCCCTGCCCCCGAGTTCGAGGGCGGACCT
AGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGA
TGATCAGCAGAACCCCCGAGGTGACCTGCGTGGTGGTGGA
CGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTAC
GTGGACGGCGTGGAAGTGCATAACGCCAAGACCAAGCCCA
GAGAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGT
GCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAA
TACAAGTGCAAGGTCTCCAACAAGGGCCTGGCCAGCAGCA
TCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGA
GCCCCAGGTCTGCACCCTGCCACCTAGCCAAGAGGAGATG
ACCAAGAACCAGGTGTCCCTGAGCTGTGCCGTGAAAGGCT
TCTATCCCAGCGATATCGCCGTGGAGTGGGAGAGCAACGG
CCAGCCCGAGAACAACTACAAGACCACCCCCCCCTGTGCTG
GACAGCGACGGCAGCTTCTTCCTGGTTTCCAAGCTGACCG
TGGACAAGTCCAGATGGCAGGAGGGCAACGTCTTCAGCTG
CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAG
AAGTCCCTGAGCCTGAGCCTGGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 58
QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQ
KPGQAPRGLIGGTNKRAPWTPARFSGSLLGGKAALTITGA
QAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVTL
FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH
EGSTVEKTVAPTECS

Nucleotide sequence: SEQ ID NO. 59
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTC
CTGGCGGCACAGTGACCCTGACCTGTAGATCTTCTACAGG
CGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGCAG
AAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAA
ACAAGAGAGCCCCTTGGACACCCGCCAGATTCTCTGGATC
TCTGCTCGGCGGAAAGGCCGCTCTGACAATCACTGGTGCT
CAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGT
ACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAACTGAC
AGTTCTGGGTCAGCCCAAGGCGGCGCCCTCGGTCACTCTG
TTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCA
CACTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGT
GACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCG
GGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACA
AGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCA
GTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCAT
GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAAT
GTTCA

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 60
EVOLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQA
PGKGLEWVGRIRSKYNNYATYYADSVKDRFTISRDDSKNS
LYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQGTL
VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFE
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF
NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQ
EEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGK

TABLE 3-continued

Sequences of anti-CD20×CD3 κλ bispecific antibodies

Nucleotide sequence: SEQ ID NO. 61
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC
CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT
CACCTTCAACACCTACGCTATGAACTGGGTCCGACAGGCC
CCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCA
AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA
GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACAGC
CTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCG
CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG
CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG
GTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGT
TCCCCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCAC
AGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG
CCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCG
GCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACT
GTACTCCCTGAGCAGCGTGGTGACCGTGCCTTCCAGCAGC
CTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGC
CCAGCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTA
CGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCGAG
GGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGG
ACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGT
GGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTT
AATTGGTACGTGGACGGCGTGGAAGTGCATAACGCCAAGA
CCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAGAGT
GGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAAC
GGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGGCCTGG
CCAGCAGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCA
GCCACGGGAGCCCCAGGTCTACACCCTGCCACCTTGTCAA
GAGGAGATGACCAAGAACCAGGTGTCCCTGTGGTGTCTGG
TGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGGGA
GAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCC
CCTGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCA
AGCTGACCGTGGACAAGTCCAGATGGCAGGAGGGCAACGT
CTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCAC
TACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

CD2 0×CD3 κλ005:
κ light chain of CD20 arm: SEQ ID NO. 54
EIVLTQSPGTLSLSPGERATLSCRASQSVSSYLAWYQQKP
GQAPRLLIYDASNRATGIPDRFSGSGSGTDFTLTISRLEP
EDFAVYYCQQRSNWPITFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

Nucleotide sequence: SEQ ID NO. 55
GAGATCGTGCTGACACAGAGCCCTGGCACACTGTCACTGT
CTCCAGGCGAGAGAGCCACACTGAGCTGTAGAGCCAGCCA
GAGCGTGTCCTCTTACCTGGCCTGGTATCAGCAGAAGCCT
GGACAGGCTCCCAGACTGCTGATCTACGACGCCAGCAACA
GAGCCACAGGCATCCCCGATAGATTCAGCGGCTCTGGCTC
TGGCACCGACTTCACCCTGACAATCAGCAGACTGGAACCC
GAGGACTTCGCCGTGTACTACTGCCAGCAGAGGAAGCAACT
GGCCCATCACATTCGGCCAGGGCACCAAGCTGGAAATCAA
GCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCA
TCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACA
GCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GT

Heavy chain (heavy chain 1) of CD20 arm: SEQ ID NO. 56
EVQLLESGGGVVQPGGSLRLSCAASGFTFNDYAMHWVRQA
PGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNSKNTLY
LQMNSLRAEDTAVYYCAKDIQYGNYYYGMDYWGQGTLVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE

TABLE 3-continued

Sequences of anti-CD20×CD3 κλ bispecific antibodies

YKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEM
TKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK

Nucleotide sequence: SEQ ID NO. 57
GAAGTGCAGCTGCTGGAATCTGGTGGCGGAGTTGTTCAGC
CTGGCGGCTCTCTGAGACTGTCTTGTGCTGCCAGCGGCTT
CACCTTCAACGACTACGCTATGCACTGGGTCCGACAGGCC
CCTGGCAAAGGACTTGAATGGGTGTCCACCATCAGCTGGA
ACAGCGGCTCTATCGGCTACGCCGATTCCGTGAAGGGCAG
ATTCACCATCTCCAGAGACAACAGCAAGAACACCCTGTAC
CTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGT
ACTACTGTGCCAAGGACATCCAGTACGGCAACTACTACTA
CGGCATGGACTACTGGGGCCAGGGAACACTGGTTACCGTT
AGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGG
CCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCT
GGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC
GTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCATA
CCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCT
GAGCAGCGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACC
AAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACA
CCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTCC
CTGCCCCCCTTGCCCTGCCCCCGAGTTCGAGGGCGGACCT
AGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGA
TGATCAGCAGAACCCCCGAGGTGACCTGCGTGGTGGTGGA
CGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTAC
GTGGACGGCGTGGAAGTGCATAACGCCAAGACCAAGCCCA
GAGAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGT
GCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAA
TACAAGTGCAAGGTCTCCAACAAGGGCCTGGCCAGCAGCA
TCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGA
GCCCCAGGTCTGCACCCTGCCACCTAGCCAAGAGGAGATG
ACCAAGAACCAGGTGTCCCTGAGCTGTGCCGTGAAAGGCT
TCTATCCCAGCGATATCGCCGTGGAGTGGGAGAGCAACGG
CCAGCCCGAGAACAACTACAAGACCACCCCCCCCTGTGCTG
GACAGCGACGGCAGCTTCTTCCTGGTTTCCAAGCTGACCG
TGGACAAGTCCAGATGGCAGGAGGGCAACGTCTTCAGCTG
CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAG
AAGTCCCTGAGCCTGAGCCTGGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 66
QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQE
KPGQAPRGLIGGTNKRAPWTPARFSGSLLGGKAALTITGA
QAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVTL
FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH
EGSTVEKTVAPTECS

Nucleotide sequence: SEQ ID NO. 67
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTC
CTGGCGGCACAGTGACCCTGACCTGTAGATCTTCTACAGG
CGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGGAG
AAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAA
ACAAGAGAGCCCCTTGGACACCCGCCAGATTCTCTGGATC
TCTGCTCGGCGGAAAGGCCGCTCTGACAATCACTGGTGCT
CAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGT
ACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAACTGAC
AGTTCTGGGTCAGCCCAAGGCGGCGCCCTCGGTCACTCTG
TTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCA
CACTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGT
GACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCG
GGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACA
AGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCA
GTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCAT
GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAAT
GTTCA

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 68
EVOLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRKA
PGKGLEWVGRIRSKYNNYATYYADSVKDRFTISRDDSKNS
LYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQGTL
VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE

TABLE 3-continued

Sequences of anti-CD20×CD3 κλ bispecific antibodies

PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFE
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF
NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQ
EEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 69
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC
CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT
CACCTTCAACACCTACGCTATGAACTGGGTCCGAAAGGCC
CCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCA
AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA
GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACAGC
CTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCG
CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG
CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG
GTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGT
TCCCCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCAC
AGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG
CCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCG
GCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACT
GTACTCCCTGAGCAGCGTGGTGACCGTGCCTTCCAGCAGC
CTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGC
CCAGCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTA
CGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCGAG
GGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGG
ACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGT
GGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTT
AATTGGTACGTGGACGGCGTGGAAGTGCATAACGCCAAGA
CCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAGAGT
GGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAAC
GGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGGCCTGG
CCAGCAGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCA
GCCACGGGAGCCCCAGGTCTACACCCTGCCACCTTGTCAA
GAGGAGATGACCAAGAACCAGGTGTCCCTGTGGTGTCTGG
TGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGGGA
GAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCC
CCTGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCA
AGCTGACCGTGGACAAGTCCAGATGGCAGGAGGGCAACGT
CTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCAC
TACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

CD2 0×CD3-crossFab
κ light chain of CD20 arm: SEQ ID NO. 70
EIVLTQSPGTLSLSPGERATLSCRASQSVSSYLAWYQKKP
GQAPRLLIYDASNRATGIPDRFSGSGSGTDFTLTISRLEP
EDFAVYYCQQRSNWPITFGQGTKLEIKRTVAAPSVFIFPP
SDKKLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

Nucleotide sequence: SEQ ID NO. 71
GAGATCGTGCTGACACAGAGCCCTGGCACACTGTCACTGT
CTCCAGGCGAGAGAGCCACACTGAGCTGTAGAGCCAGCCA
GAGCGTGTCCTCTTACCTGGCCTGGTATCAGAAGAAGCCT
GGACAGGCTCCCAGACTGCTGATCTACGACGCCAGCAACA
GAGCCACAGGCATCCCCGATAGATTCAGCGGCTCTGGCTC
TGGCACCGACTTCACCCTGACAATCAGCAGACTGGAACCC
GAGGACTTCGCCGTGTACTACTGCCAGCAGAGAAGCAACT
GGCCCATCACATTCGGCCAGGGCACCAAGCTGGAAATCAA
GCGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCA
TCTGATAAGAAATTGAAATCTGGAACTGCCTCTGTTGTGT
GCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACA
GCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
GAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GT

TABLE 3-continued

Sequences of anti-CD20×CD3 κλ bispecific antibodies

Heavy chain (heavy chain 1) of CD20 arm: SEQ ID NO. 74

EVQLLESGGGVVQPGGSLRLSCAASGFTFNDYAMHWVREA
PGKGLEWVSTISWNSGSIGYADSVKGRFTISRDNSKNTLY
LQMNSLRAEDTAVYYCAKDIQYGNYYYGMDYWGQGTLVTV
SSASTKGPSVFPLAPCSRSTSESTAALGCLVEDYFPEPVT
VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDERVESKYGPPCPPCPAPEFEGGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFASTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLPSSIEKTISKAKGQPREPQVCTLPPSQEEM
TKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLVSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK

Nucleotide sequence: SEQ ID NO. 75

GAAGTGCAGCTGCTGGAATCTGGTGGCGGAGTTGTTCAGC
CTGGCGGCTCTCTGAGACTGTCTTGTGCTGCCAGCGGCTT
CACCTTCAACGACTACGCTATGCACTGGGTCCGAGAGGCC
CCTGGCAAAGGACTTGAATGGGTGTCCACCATCAGCTGGA
ACAGCGGCTCTATCGGCTACGCCGATTCCGTGAAGGGCAG
ATTCACCATCTCCAGAGACAACAGCAAGAACACCCTGTAC
CTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCCGTGT
ACTACTGTGCCAAGGACATCCAGTACGGCAACTACTACTA
CGGCATGGACTACTGGGGCCAGGGAACACTGGTTACCGTT
AGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGG
CCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCT
GGGCTGCCTGGTGGAGGACTACTTCCCCGAGCCCGTGACC
GTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCATA
CCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCT
GAGCAGCGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACC
AAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACA
CCAAGGTGGACGAGAGAGTGGAGAGCAAGTACGGCCCTCC
CTGCCCCCCTTGCCCTGCCCCCGAGTTCGAAGGCGGACCT
AGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGA
TGATCAGCAGAACCCCCGAGGTGACCTGCGTGGTGGTGGA
CGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTAC
GTGGACGGCGTGGAAGTGCATAACGCCAAGACCAAGCCCA
GAGAGGAGCAGTTCGCCAGCACCTACAGAGTGGTGTCCGT
GCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAA
TACAAGTGCAAGGTCTCCAACAAGGGCCTGCCTAGCAGCA
TCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGA
GCCCCAGGTCTGCACCCTGCCCACCTAGCCAAGAGGAGATG
ACCAAGAACCAGGTGTCCCTGAGCTGTGCCGTGAAAGGCT
TCTATCCCAGCGATATCGCCGTGGAGTGGGAGAGCAACGG
CCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTG
GACAGCGACGGCAGCTTCTTCCTGGTTTCCAAGCTGACCG
TGGACAAGTCCAGATGGCAGGAGGGCAACGTCTTCAGCTG
CTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAG
AAGTCCCTGAGCCTGAGCCTGGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 76

EVOLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRKA
PGKGLEWVGRIRSKYNNYATYYADSVKDRFTISRDDSKNS
LYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQGTL
VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE
PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTKTYTCNVDHKPSNTKVDKRV

Nucleotide sequence: SEQ ID NO. 77

GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGC
CTGGCGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTT
CACCTTCAACACCTACGCTATGAACTGGGTCCGAAAGGCC
CCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCA
AGTACAACAACTACGCCACCTACTACGCCGACAGCGTGAA
GGACAGATTCACCATCAGCAGGGACGACAGCAAGAACAGC
CTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCG
CCGTGTACTACTGTGTCAGACACGGCAACTTCGGCAACAG
CTATGTGTCTTGGTTTGCCTACTGGGGCCAGGGCACACTG
GTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGT
TCCCCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCAC
AGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG
CCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCG

TABLE 3-continued

Sequences of anti-CD20×CD3 κλ bispecific antibodies

GCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACT
GTACTCCCTGAGCAGCGTGGTGACCGTGCCTTCCAGCAGC
CTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGC
CCAGCAACACCAAGGTGGACAAGAGAGTG

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 78

QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQE
KPGQAPRGLIGGTNKRAPWTPARFSGSLLGGKAALTITGA
QAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVTL
FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA
GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH
EGSTVEKTVAPTECSESKYGPPCPPCPAPEFEGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
VHNAKTKPREEQFASTYRVVSVLTVLHQDWLNGKEYKCKV
SNKGLPSSIEKTISKAKGQPREPQVYTLPPCQEEMTKNQV
SLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL
SLGK

Nucleotide sequence: SEQ ID NO. 79

CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTC
CTGGCGGCACAGTGACCCTGACCTGTAGATCTTCTACAGG
CGCCGTGACCACCAGCAACTACGCTAATTGGGTGCAGGAG
AAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAA
ACAAGAGAGCCCCTTGGACACCCGCCAGATTCTCTGGATC
TCTGCTCGGCGGAAAGGCCGCTCTGACAATCACTGGTGCT
CAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGT
ACAGCAACCTGTGGGTGTTCGGCGGAGGCACCAAACTGAC
AGTTCTGGGTCAGCCCAAGGCGGCGCCCTCGGTCACTCTG
TTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCA
CACTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGT
GACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCG
GGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACA
AGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCA
GTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCAT
GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAAT
GTTCAGAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCC
TGCCCCCGAGTTCGAGGGCGGACCTAGCGTGTTCCTGTTC
CCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGAACCC
CCGAGGTGACCTGCGTGGTGGTGGACGTGTCCCAGGAGGA
CCCCGAGGTCCAGTTTAATTGGTACGTGGACGGCGTGGAA
GTGCATAACGCCAAGACCAAGCCCAGAGAGGAGCAGTTCG
CCAGCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCA
CCAGGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTC
TCCAACAAGGGCCTGCCTAGCAGCATCGAGAAGACCATCA
GCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTCTACAC
CCTGCCACCTTGTCAAGAGGAGATGACCAAGAACCAGGTG
TCCCTGTGGTGTCTGGTGAAAGGCTTCTATCCCAGCGATA
TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAA
CTACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGC
TTCTTCCTGTACTCCAAGCTGACCGTGGACAAGTCCAGAT
GGCAGGAGGGCAACGTCTTCAGCTGCTCCGTGATGCACGA
GGCCCTGCACAACCACTACACCCAGAAGTCCCTGAGCCTG
AGCCTGGGCAAG

2. Expression and Purification of Anti-CD20×CD3 κλ Bispecific Antibodies

[0254] The plasmids encoding the corresponding antibody fragments were mixed with CD20 arm light chain: CD3 arm light chain: CD20 arm heavy chain (heavy chain 1): CD3 arm heavy chain (heavy chain 2)=2:2:1:1 ratio. After mixing with 3 mg/mL PEI, CHO-S cells were performed with co-transfect, culture in 500 mL CD CHO AGT medium (Gibco #12490-001) at 37° C., 5% CO2, 150 rpm, and addon of 4% CHO Feed C+supplement (Gibco #A25031-05) at transient day 2, 4 and 6, respectively. When the cell viability decreased to about 85%, the fermentation broth was harvested, filtered and purified by Protein A affinity chroma-

tography. With the anti-CD20×CD3 κλ bispecific antibody constructed on the basis of different light chain types, the monomer purity after one-step purification of Protein A was close to or higher than 90%, while the monomer purity of the control antibody CD20×CD3-crossFab was lower than 80% (Table 4), and the ratio of κλ light chains was close to 1:1 (FIG. **6**).

TABLE 4

Purity of anti-CD20 × CD3 κλ bispecific antibodies (SEC-HPLC)

	SEC-HPLC(%)		
Bispecific antibody	Mer	Monomer	Fragment
CD20 × CD3 κλ001	4.1	92.5	3.5
CD20 × CD3 κλ002	4.6	90.8	4.5
CD20 × CD3 κλ003	3.1	88.3	8.6
CD20 × CD3 κλ004	4.8	91.1	4.0
CD20 × CD3 κλ005	6.0	90.5	3.5
CD20 × CD3-crossFab	7.6	76.0	16.4

[0255] The anti-CD20×CD3 κλ bispecific antibody was further purified by purification using Capto S ImpAct ion exchange chromatography, eluting through a 50-300 mM NaCl, 50 mM phosphate, pH6.4 gradient, pooling the elution peaks and showing greater than 99% SEC-HPLC monomer content (FIG. **7**). In the purified samples of CD20×CD3 κλ002 and CD20×CD3 κλ003, the light chain mismatch ratio was very low (<1%) and no CD3 homodimers or CD20 homodimers were detected (FIG. **8**).

3. Binding Activity of Anti-CD20×CD3 κλ Bispecific Antibodies

[0256] The affinity of the bispecific antibody CD20 antigen arm was determined by measuring binding to CD20 over-expressing stably transfected cells or CD20+ tumor cells, respectively, and the affinity of the bispecific antibody CD3 arm was determined by measuring binding to CD3 recombinant antigen, Jurkat cells, or freshly isolated peripheral blood T-cells. The results showed that the affinity of the novel anti-CD20×CD3κλ bispecific antibody to tumor cells was about 3-5 times higher than that to T-cells. The positive control antibody bsAB1 was synthesized and expressed as described in US20170174781.

(1) Binding of Anti-CD20×CD3 κλ Bispecific Antibodies to Human and Cynomolgus Monkey CD20 Stably Transfected Cells

[0257] CHO-human CD20 and CHO-cynomolgus monkey CD20 stably transfected cells prepared in Example 1 in logarithmic growth phase were adjusted to 5×105 cells/ml with 4% calf serum (Hyclone, SH30626.06), 100 μl/well cell suspension was added to 96-well U-plate, 300 g thereof was centrifuged for 5 min, the supernatant was discarded, and 100 μL of gradient diluted antibody (with starting concentration of 1800 nM, 3-fold dilution, 10 gradients) was added to each well and incubated at 4° C. for 60 min. 50 μL/well Alexa Fluro647 labeled goat anti-human IgG Fc (1: 300 dilution) was added to the secondary antibody and incubated on ice for 20 min. After washing once, 50 μL/well propidium iodide (PI) solution (1: 300) was added, incubated for 5 min, and performed with detection by flow cytometry. FIG. **9** and Table 5 show that the anti-CD20×CD3 κλ bispecific antibody binds with high affinity to the cellular CD20 receptor with comparable affinity on human and cynomolgus monkey CD20 stably transfected cells.

TABLE 5

Binding of anti-CD20 × CD3 κλ bispecific antibodies to CD20 stably transfected cells.

EC_{50}	Human CD20-CHO	Cynomolgus monkey CD20-CHO
CD20 × CD3 κλ001	10 nM	12 nM
CD20 × CD3 κλ002	9 nM	8 nM
CD20 × CD3 κλ003	7 nM	8 nM
CD20 × CD3 κλ004	8 nM	10 nM
CD20 × CD3 κλ005	9 nM	14 nM
KLH × CD3	—	—

"—": not combined with

(2) Binding of Anti-CD20×CD3 κλ Bispecific Antibody to Human CD20+Tumor Cells

[0258] The SU-DHL-4, Raji and NALM-6 cells were taken in logarithmic growth phase, added with 200 μg/mL murine IgG (Jackson ImmunoResearch, 115-005-03) to ice bath for blocking for 30 min, the cells were adjusted to 5×10^5 cells/mL with 4% calf serum, and 100 μL/well was added to 96-well U-plate, 300 g was centrifuged for 5 min, discarding the supernatant. 100 μL/well of gradient diluted antibody (initial concentration: 1800 nM, 3-fold dilution, 10 gradients) was added, and incubated at 4° C. for 60 min. The primary antibody was washed off, 50 μL/well Alexa Fluro647-labeled goat anti-human IgG Fc (1: 300 dilution) was added and incubated on ice for 20 min. 50 μL/well PI was added after washing once, incubated for 5 min, and detected with flow cytometer. The results are shown in FIG. **10** and Table 6. The anti-CD20×CD3 κλ bispecific antibody binds with high affinity to CD20+ tumor cells SU-DHL-4, Raji and NALM-6.

(3) Binding of Anti-CD20×CD3 κλ Bispecific Antibody to Jurkat Cells

[0259] Jurkat cells in logarithmic growth phase were added with 200 μg/mL murine IgG (Jackson ImmunoResearch, 115-005-03) and incubated on ice for 30 minutes. The cells were adjusted to 5×10^5 cells/mL with 4% calf serum, 100 μL/well was added to 96-well U-plate, 300 g was centrifuged to removed the supernatant, 100 μL/well of gradient diluted antibody (initial concentration: 1800 nM, 3-fold dilution, 10 gradients) was added and incubated at 4° C. for 60 min. 50 μL/well Alexa Fluro647-labeled goat anti-human IgG Fc (1: 300 dilution) was added to the secondary antibody and incubated on ice for 20 min. 50 μL/well PI was added after washing once, incubated for 5 min, and detected with flow cytometer (BD C6). As shown in FIG. **11** and Table 6, the anti-CD20×CD3 κλ bispecific antibody binds with moderate affinity to human leukemia T-cell line Jurkat cells with an EC_{50} of about 71-120 nM, which is about 10-fold lower than the binding of the CD20 antigen arm to the CD20 receptor.

(4) Binding of Anti-CD20×CD3 κλ Bispecific Antibody to Human Peripheral Blood T-Cells

[0260] Human fresh peripheral blood was taken and PBMC was isolated by Ficoll. Paque Plu (GE, 17-1440-03).

PBMC was adjusted to 5×10^5 cells/mL with 4% calf serum (Hyclone, SH30626.06), 100 μL/well was added to a 96-well U-plate, the supernatant was centrifuged off and 100 μL of gradient diluted antibody (with starting concentration of 1800 nM, 3-fold dilution, 10 gradients) was added to each well and incubated for 60 min at 4° C. 50 μL/well of Alexa Fluro647 labeled goat anti-human IgG Fc (1: 300 dilution) was added to the secondary antibody, with ice bath for 20 min, and 50 μL/well PI added after washing once, incubated for 5 min, and flow cytometer (BD C6) was used for detection. The detection results are shown in FIG. **12** and Table 6. The anti-CD20×CD3 κλ bispecific antibody recognizes human peripheral blood $CD4^+$T and $CD8^+$T-cells, has an affinity of about 65-98 nM with human T-cells, is weaker than the binding force of CD20 antigen arm with CD20 receptor by about 10 times, and favors the preferential enrichment of the bispecific antibody to tumor cells.

TABLE 6

Binding capacity (nM) of anti-CD20 × CD3 κλ bispecific antibodies to human cells

EC_{50} (nM)	SU-DHL-4	Raji	NALM-6	Jurkat	CD4T	CD8T
CD20 × CD3 κλ002	7	23	10	71	73	98
CD20 × CD3 κλ003	6	25	8	120	69	65
bsAB1	19	115	48	ND	25	22
KLH × CD3	—	—	—	33	62	65

ND: not saturated at high concentration

4. TDCC Mediated by Anti-CD20×CD3 κλ Bispecific Antibody

[0261] Freshly isolated PBMC was mixed with target cells NALM-6, TMD-8 and Toledo cells in logarithmic growth phase, with effect/target cell=8: 1, respectively. 50 μL of gradient diluted antibody (antibody concentration from 66.7 nM, 10-fold dilution, 7 gradients) was added to each well, and incubated for 24 h at 37° C. in 5% CO_2. At the end of the incubation, 50 μL of the supernatant was transferred to a new black elisa plate, 50 μL/well of LDH detection substrate was added, the reaction was stopped after 10 minutes and LDH release was detected. The remaining cells in the wells were washed twice with 4% calf blood, incubated with 100 μg/mL human IgG for 10 minutes, followed by T-cell activation detection antibodies (CD25-PE, CD4-APC, CD69-FITC and CD8-APC) and incubated on ice for 20 minutes. The supernatant was washed and discarded, 60 μL/well PI was added, incubated on ice for 5 minutes and detected by flow cytometry. FIGS. **13**A, **13**B show the killing of human B-lymphoblastic leukemia cells Nalm-6 by the anti-CD20×CD3 κλ bispecific antibody and the activation of T-cells, respectively. FIGS. **14**A, **14**B show killing of TMD-8 cells and activation of T-cells by the anti-CD20×CD3κλ bispecific antibody, respectively. FIGS. **15**A, **15**B show killing of Toledo cells and activation of T-cells by a CD20×CD3κλ bispecific antibody, respectively. For tumor cells Nalm-6, TMD-8 and Toledo with different CD20 expression levels, both CD20×CD3×κλ002 and CD20×CD3×κλ003 could mediate effective killing of T-cells, with killing activity comparable to or slightly stronger than that of control antibody bsAB1, and the activation of T-cells was milder than the latter. 5. Activation of T-cell activation pathway by anti-CD20×CD3 κλ bispecific antibody Logarithmically growing Jurkat-NFAT-luc reporter cells and CD20-positive target cells (SU-DHL-4, raji and NALM-6 cells) were taken, centrifuged, with the supernatant discarded and resuspended to 2×106 cells/ml. 50p/well of the target cells were inoculated into a 96-well plate, the supernatant was discarded by centrifugation at 300 g for 5 minutes, and 50l/well of the Jurkat-NFAT-luc reporter cells were inoculated into a 96-well plate, and 50 μl of gradient-diluted CD20×CD30, bispecific antibody or control antibody KLH×CD3 (initial concentration of 20 μg/ml, 10-fold dilution, 10 gradients) was added to each well, and incubated at 37° C. for 6 hours in 5% CO_2. After the incubation, 100 μL of detection reagent was added to each well according to ONE-Glo Luciferase Assay System instructions, allowed to stand at room temperature for 3 minutes, and detected on a microplate reader (Biotek Synergy HT). The detection results are shown in FIG. **16** and Table 7. The CD20×CD30, bispecific antibody can activate the NFAT signaling pathway of T-cells when tumor cells with different CD20 expression levels are used as target cells.

TABLE 7

Activation of the T-cell NFAT pathway by the anti-CD20 × CD3 κλ bispecific antibody.

EC_{50}(nM)	SU-DHL-4	Raji	NALM-6
CD20 × CD3 κλ002	0.10	0.02	0.14
CD20 × CD3 κλ003	0.11	0.02	0.14
KLH × CD3	—	—	—

6. Binding of Anti-CD20×CD3 κλ Bispecific Antibodies to Fcγ Receptors

[0262] 50 Mg/ml of His-Tag antibody was amino-conjugated to a CM5 chip to capture the His-tagged FcγRI, $Fc\gamma RIIA_{H131}$ and $Fc\gamma RIIIA_{V158}$ recombinant proteins (Sino Biological, #10256-H08H/10374-H08H1/10389-H08H1), respectively, with a capture time of 40 seconds and a flow rate of 10 μL/min. After baseline plateau, the gradient diluted antibody (with starting concentration of 37.5 μg/mL, 2-fold dilution) was flowed through the chip at a flow rate of 30 μL/min, with an association time of 120 seconds and a dissociation time of 200 seconds, and affinity constants were obtained by fitting with Biacore evaluation software. As can be seen from Table 8, the CD20×CD3κλ bispecific antibody did not bind to FcγRI, $Fc\gamma RIIA_{H131}$ and $Fc\gamma RIIIA_{V158}$; the wild-type IgG4 control antibody bound FcγRI with high affinity and weakly bound to $Fc\gamma RIIA_{H131}$.

TABLE 8

Affinities of anti-CD20 × CD3 κλ bispecific antibodies to Fcγ receptors

KD	FcγRI	$FcγRIIA_{H131}$	$FcγRIIIA_{V158}$
CD20 × CD3 κλ002	Not combined	Not combined	Not combined
CD20 × CD3 κλ003	Not combined	Not combined	Not combined
IgG4 isotype control	14 nM	Weak	Not combined

7. Immune Reconstitution of Subcutaneous Raji Tumor Model in Mice

[0263] Six to eight-week-old female B-NGD mice (Bio-Tech Co. Ltd.) were subcutaneously inoculated with 3×10^6 Raji cells. When the tumors grew to 60 mm^3, they were randomly divided into treatment group 3.0 mg/kg, treatment group 0.6 mg/kg, treatment group 0.12 mg/kg and a negative control group with KLH×CD3 of 3 mg/kg. Each mouse received 1×10^7 PBMC cells via tail vein injection. Three days later, the first dose was administered to the mouse once every 5 days for a total of 3 doses. The tumor volume and body weight of the mice were monitored. At the end of the experiment, the mice were killed by cervical dislocation and the tumors were collected and weighed. The results are shown in FIG. **17**. The in vivo efficacy of anti-CD20×CD3 κλ bispecific antibody was dose-related, with tumor inhibition rates of 82% and 89% at medium and high doses, respectively. The tumor-bearing mice tolerated the foregoing doses well, without weight loss and other adverse reactions.

8. Subcutaneous Tumor Model Grafted by a Mixture of Murine Raji and Human PBMC in Immunodeficient Mice

[0264] 6-8 week female B-NGD mice (Bio-Oracle Bio-Tech Co. Ltd.) were selected, Raji (3×10^6) and human PBMC (5×10^6) were mixed and inoculated subcutaneously. When the tumor volume reaches 60-100 mm^3, they were randomly divided into groups. The dose groups were respectively set as dose group of 3.0 mg/mL, dose group of 0.6 mg/mL, dose group of 0.12 mg/mL and negative control group of KLH×CD3 of 3 mg/kg. The dosing interval was once every 5 days for a total of 2 doses. The tumor volume and body weight of the mice were monitored. At the end of the experiment, the mice were killed by cervical dislocation and the tumors were collected and weighed. The results are shown in FIG. **18**. The in vivo efficacy of anti-CD20×CD3 κλ, bispecific antibody was dose-related, with tumor inhibition rates of 65%, 98% and 162% at low, medium and high doses, respectively. The tumor was completely inhibited or subsided in high and medium dose groups.

9. Efficacy of Anti-CD20×CD3 κλ Bispecific Antibody in Cynomolgus Monkeys

[0265] Eight cynomolgus monkeys were assigned to 4 dose groups, each dose group consisted of 2 monkeys, half males and half females. Each dose group received doses of 0.3, 1 and 3 mg/kg (once a week for 3 weeks, a total of 4 doses) and 1 mg/kg (single dose) of CD20×CD3 κλ002 bispecific antibody. See Table 9 for dosing schedule. During the administration period and recovery period, all monkeys in each group were in good general condition, without toxic reaction or death or moribund. No significant abnormal change in body temperature was observed in each dose group, and lead II ECG waveform was normal. There was no significant abnormality in heart rate, R-R interval, β-R interval, QT interval, QRS time limit, systolic blood pressure and diastolic blood pressure. Changes in the number of B and T-cell populations in peripheral blood were analyzed by flow cytometry at various time points after administration, with B cells identified using the cell surface marker CD20 (CD20+cells) and T-cells identified using CD3 (CD3+ cells). B cells were rapidly cleared from peripheral blood at 8 hours post-dose and were below the lower detection limit at 24 hours (FIG. **19**).

TABLE 9

CD20 × CD3 κλbispecific antibody dosing regimen

Group	Dose	Route and frequency of administration	Gender	Animal Number
Low dose group	0.3 mg/kg	IV, one time per week/3 weeks, D 1, D 8, D 15, D 22	Male Female	2016221 2016222
Medium dose group	1 mg/kg	IV, one time per week/3 weeks, D 1, D 8, D 15, D 22	Male Female	2016223 2016224
High dose group	3 mg/kg	IV, one time per week/3 weeks, D 1, D 8, D 15, D 22	Male Female	2016225 2016226
Medium dose group	1 mg/kg	IV, Single dose on D 1	Female Male	2016227 2016228

Example 3: Construction of BCMA×CD3 κλ Bispecific Antibodies Formed by Different Types of Light Chains

1. Construction of BCMA×CD3 Bispecific Antibody

[0266] A novel BCMA-CD3 κλ humanized bispecific antibody having the native IgG configuration was constructed with a κ light chain-containing BCMA humanized antibody, and a λ light chain-containing humanized CD3 antibody, with reference to example 2, while charge variants are introduced in the BCMA antigen and the CD3 arm ($V\kappa_{BCMA}$: $Gln_{42}Lys$; VH_{BCMA}: $Gln_{39}Glu$; $V\lambda_{CD3}$: $Gln_{40}Glu$; VH_{CD3}: $Gln_{39}Lys$) (see Table 10 for sequence); the Fc portion of the bispecific antibody adopts the human IgG4 knob-into-hole structure to achieve heterodimer pairing, and through mutation of $Ser_{228}Pro$, $Leu_{235}Glu$ and $Pro_{329}Ala$, the hinge region remains stable and interaction with FcγR receptor and Clq is reduced.

TABLE 10

BCMA × CD3 κλbispecific antibodies

Protein sequence	light chain of BCMA arm	heavy chain of BCMA arm	light chain of CD3 arm	heavy chain of CD3 arm
BCMA × CD3 κλ003	SEQ ID NO. 80	SEQ ID NO. 82	SEQ ID NO. 66	SEQ ID NO. 68
BCMA × CD3 κλ004	SEQ ID NO. 84	SEQ ID NO. 82	SEQ ID NO. 66	SEQ ID NO. 68
BCMA × CD3 κλ005	SEQ ID NO. 80	SEQ ID NO. 86	SEQ ID NO. 66	SEQ ID NO. 68
BCMA × CD3 κλ006	SEQ ID NO. 84	SEQ ID NO. 86	SEQ ID NO. 66	SEQ ID NO. 68

BCMA × CD3 κλ003

κ light chain of BCMA arm: SEQ ID NO. 80

DIVLTQSPASLAVSPGQRATITCRASKSVSTSGYSYMHWYQKKPGQPPKLLIYLASNLESG
VPARFSGSGSGTDFTLTINPVEAEDTANYYCQHSRELPWTFGQGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Nucleotide sequence: SEQ ID NO. 81

GACATCGTGCTGACACAGAGCCCTGCTTCTCTGGCTGTGTCTCCTGGCCAGAGAGCCA
CCATCACCTGTAGAGCCAGCAAGAGCGTGTCCACCAGCGGCTACTCTTACATGCACTG
GTATCAGAAGAAGCCCGGCCAGCCTCCTAAGCTGCTGATCTACCTGGCTAGCAACCTC
GAAAGCGGAGTGCCTGCTAGATTTTCTGGCAGCGGCTCTGGCACCGACTTCACCCTGA
CAATCAACCCCGTGGAAGCCGAAGACACCGCCAACTACTACTGCCAGCACAGCAGAG
AGCTGCCCTGGACATTTGGCCAGGGCACCAAGGTGGAAATCAAGCGAACTGTGGCTG
CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCT
GTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGG
ATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGG
ACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGA
GCTTCAACAGGGGAGAGTGT

Heavy chain (heavy chain 1) of BCMA arm: SEQ ID NO. 82

QVQLVQSGSELKKPGASVKVSCKASGYIFTNFGMNWVREAPGQGLEWMGWINTYTGEQ
IYADGFTGRFVFSLDTSASTAYLQISSLKAEDTAVYFCARGEIYYGYDVGFVYWGQGTLVT
VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEMTK
NQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 83

CAGGTTCAGCTGGTGCAGTCTGGCAGCGAGCTGAAGAAACCTGGCGCCTCTGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACATCTTCACCAACTTCGGCATGAACTGGGTCCGAG
AGGCTCCTGGACAGGGACTCGAATGGATGGGCTGGATCAACACCTACACCGGCGAGC
AGATCTACGCCGATGGCTTCACAGGCAGATTCGTGTTCAGCCTGGACACCAGCGCCAG
CACAGCTTACCTGCAGATCAGCTCTCTGAAGGCCGAGGATACCGCCGTGTACTTCTGT
GCCAGAGGCGAGATCTACTACGGCTACGACGTGGGCTTTGTGTACTGGGGCCAGGGAA
CACTGGTCACCGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCC
TTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTA
CTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCAT
ACCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCTGAGCAGCGTGGTGACCG
TGCCTTCCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGCCCA
GCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTCCCTGCCCCCCTT
GCCCTGCCCCCGAGTTCGAGGGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAA
GGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGTC
CCAGGAGGACCCCGAGGTCCAGTTTAATTGGTACGTGGACGGCGTGGAAGTGCATAAC
GCCAAGACCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGTG
CTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCC
AACAAGGGCCTGGCCAGCAGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCC
ACGGGAGCCCCAGGTCTGCACCCTGCCACCTAGCCAAGAGGAGATGACCAAGAACCA
GGTGTCCCTGAGCTGTGCCGTGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGG
GAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGC
GACGGCAGCTTCTTCCTGGTTTCCAAGCTGACCGTGGACAAGTCCAGATGGCAGGAG
GGCAACGTCTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGA
AGTCCCTGAGCCTGAGCCTGGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 66

QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQEKPGQAPRGLIGGTNKRAPWT
PARFSGSLLGGKAALTITGAQAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVT

TABLE 10-continued

LFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSY
LSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Nucleotide sequence: SEQ ID NO. 67
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTCCTGGCGGCACAGTGACC
CTGACCTGTAGATCTTCTACAGGCGCCGTGACCACCAGCAACTACGCTAATTGGGTGC
AGGAGAAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAAACAAGAGAGCC
CCTTGGACACCCGCCAGATTCTCTGGATCTCTGCTCGGCGGAAAGGCCGCTCTGACAA
TCACTGGTGCTCAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGTACAGCAA
CCTGTGGGTGTTCGGCGGAGGCACCAAACTGACAGTTCTGGGTCAGCCCAAGGCGGC
GCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACA
CTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGTGACAGTGGCCTGGAAGGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACA
ACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACA
GAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCC
CTACAGAATGTTCA

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 68
EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRKAPGKGLEWVGRIRSKYNNYA
TYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQE
EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 69
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGCCTGGCGGATCTCTGAGA
CTGTCTTGTGCCGCCAGCGGCTTCACCTTCAACACCTACGCTATGAACTGGGTCCGAA
AGGCCCCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCAAGTACAACAACT
ACGCCACCTACTACGCCGACAGCGTGAAGGACAGATTCACCATCAGCAGGGACGACA
GCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCGCCGTGT
ACTACTGTGTCAGACACGGCAACTTCGGCAACAGCTATGTGTCTTGGTTTGCCTACTGG
GGCCAGGGCACACTGGTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCC
CCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTGG
TGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCA
GCGGCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCTGAGCAG
CGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGA
CCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTC
CCTGCCCCCCTTGCCCTGCCCCCGAGTTCGAGGGCGGACCTAGCGTGTTCCTGTTCCC
CCCCAAGCCCAAGGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGTGGT
GGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTACGTGGACGGCGT
GGAAGTGCATAACGCCAAGACCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAG
AGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAA
GTGCAAGGTCTCCAACAAGGGCCTGGCCAGCAGCATCGAGAAGACCATCAGCAAGGC
CAAGGGCCAGCCACGGGAGCCCCAGGTCTACACCCTGCCACCTTGTCAAGAGGAGAT
GACCAAGAACCAGGTGTCCCTGTGGTGTCTGGTGAAAGGCTTCTATCCCAGCGATATC
GCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCT
GTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCAAGCTGACCGTGGACAAGTCCA
GATGGCAGGAGGGCAACGTCTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACC
ACTACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

BCMA × CD3 κλ004
κ light chain of BCMA arm: SEQ ID NO. 84
DIVLTQSPASLAVSPGQRATITCRASKSVTTSGYSYIHWYQKKPGQPPKLLIYLASDLEAGV
PARFSGSGSGTDFTLTINPVEAEDTANYYCQHSRELPWTFGQGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Nucleotide sequence: SEQ ID NO. 85
GACATCGTGCTGACACAGAGCCCTGCTTCTCTGGCTGTGTCTCCTGGCCAGAGAGCCA
CCATCACCTGTAGAGCCAGCAAGAGCGTGACCACCAGCGGCTACTCTTACATCCACTG
GTATCAGAAGAAGCCCGGCCAGCCTCCTAAGCTGCTGATCTACCTGGCCAGCGATCTG
GAAGCTGGCGTGCCAGCTAGATTTTCTGGCAGCGGCTCTGGCACCGACTTCACCCTGA
CAATCAACCCCGTGGAAGCCGAAGACACCGCCAACTACTACTGCCAGCACAGCAGAG
AGCTGCCCTGGACATTTGGCCAGGGCACCAAGGTGGAAATCAAGCGAACTGTGGCTG
CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCT
GTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGG
ATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGG
ACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGA
GCTTCAACAGGGGAGAGTGT

Heavy chain (heavy chain 1) of BCMA arm: SEQ ID NO. 86
QVQLVQSGSELKKPGASVKVSCKASGYIFTNFGMNWVREAPGQGLEWMGWINTYTGEQ
IYADGFTGRFVFSLDTSASTAYLQISSLKAEDTAVYFCARGEIYYGYDVGFVYWGQGTLVT

TABLE 10-continued

VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEMTK
NQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 87
CAGGTTCAGCTGGTGCAGTCTGGCAGCGAGCTGAAGAAACCTGGCGCCTCTGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACATCTTCACCAACTTCGGCATGAACTGGGTCCGAG
AGGCTCCTGGACAGGGACTCGAATGGATGGGCTGGATCAACACCTACACCGGCGAGC
AGATCTACGCCGATGGCTTCACAGGCAGATTCGTGTTCAGCCTGGACACCAGCGCCAG
CACAGCTTACCTGCAGATCAGCTCTCTGAAGGCCGAGGATACCGCCGTGTACTTCTGT
GCCAGAGGCGAGATCTACTACGGCTACGACGTGGGCTTTGTGTACTGGGGCCAGGGAA
CACTGGTCACCGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCC
TTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTA
CTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCAT
ACCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCTGAGCAGCGTGGTGACCG
TGCCTTCCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGCCCA
GCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTCCCTGCCCCCCTT
GCCCTGCCCCCGAGTTCGAGGGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAA
GGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGTGGTGGTGGTGGACGTGTC
CCAGGAGGACCCCGAGGTCCAGTTTAATTGGTACGTGGACGGCGTGGAAGTGCATAAC
GCCAAGACCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGTG
CTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCC
AACAAGGGCCTGGCCAGCAGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCC
ACGGGAGCCCCAGGTCTGCACCCTGCCACCTAGCCAAGAGGAGATGACCAAGAACCA
GGTGTCCCTGAGCTGTGCCGTGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGG
GAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGC
GACGGCAGCTTCTTCCTGGTTTCCAAGCTGACCGTGGACAAGTCCAGATGGCAGGAG
GGCAACGTCTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGA
AGTCCCTGAGCCTGAGCCTGGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 66
QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQEKPGQAPRGLIGGTNKRAPWT
PARFSGSLLGGKAALTITGAQAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVT
LFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSY
LSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Nucleotide sequence: SEQ ID NO. 67
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTCCTGGCGGCACAGTGACC
CTGACCTGTAGATCTTCTACAGGCGCCGTGACCACCAGCAACTACGCTAATTGGGTGC
AGGAGAAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAAACAAGAGAGCC
CCTTGGACACCCGCCAGATTCTCTGGATCTCTGCTCGGCGGAAAGGCCGCTCTGACAA
TCACTGGTGCTCAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGTACAGCAA
CCTGTGGGTGTTCGGCGGAGGCACCAAACTGACAGTTCTGGGTCAGCCCAAGGCGGC
GCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACA
CTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGTGACAGTGGCCTGGAAGGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACA
ACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACA
GAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCC
CTACAGAATGTTCA

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 68
EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRKAPGKGLEWVGRIRSKYNNYA
TYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQE
EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 69
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGCCTGGCGGATCTCTGAGA
CTGTCTTGTGCCGCCAGCGGCTTCACCTTCAACACCTACGCTATGAACTGGGTCCGAA
AGGCCCCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCAAGTACAACAACT
ACGCCACCTACTACGCCGACAGCGTGAAGGACAGATTCACCATCAGCAGGGACGACA
GCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCGCCGTGT
ACTACTGTGTCAGACACGGCAACTTCGGCAACAGCTATGTGTCTTGGTTTGCCTACTGG
GGCCAGGGCACACTGGTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCC
CCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTGG
TGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCA
GCGGCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCTGAGCAG
CGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGA
CCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTC
CCTGCCCCCCTTGCCCTGCCCCCGAGTTCGAGGGCGGACCTAGCGTGTTCCTGTTCCC

TABLE 10-continued

CCCCAAGCCCAAGGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGTGGT
GGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTACGTGGACGGCGT
GGAAGTGCATAACGCCAAGACCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAG
AGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAA
GTGCAAGGTCTCCAACAAGGGCCTGGCCAGCATCGAGAAGACCATCAGCAAGGC
CAAGGGCCAGCCACGGGAGCCCCAGGTCTACACCCTGCCACCTTGTCAAGAGGAGAT
GACCAAGAACCAGGTGTCCCTGTGGTGTCTGGTGAAAGGCTTCTATCCCAGCGATATC
GCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCT
GTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCAAGCTGACCGTGGACAAGTCCA
GATGGCAGGAGGGCAACGTCTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACC
ACTACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

BCMA x CD3 κλ005
κ light chain of BCMA arm: SEQ ID NO. 80
DIVLTQSPASLAVSPGQRATITCRASKSVSTSGYSYMHWYQKKPGQPPKLLIYLASNLESG
VPARFSGSGSGTDFTLTINPVEAEDTANYYCQHSRELPWTFGQGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Nucleotide sequence: SEQ ID NO. 81
GACATCGTGCTGACACAGAGCCCTGCTTCTCTGGCTGTGTCTCCTGGCCAGAGAGCCA
CCATCACCTGTAGAGCCAGCAAGAGCGTGTCCACCAGCGGCTACTCTTACATGCACTG
GTATCAGAAGAAGCCCGGCCAGCCTCCTAAGCTGCTGATCTACCTGGCTAGCAACCTC
GAAAGCGGAGTGCCTGCTAGATTTTCTGGCAGCGGCTCTGGCACCGACTTCACCCTGA
CAATCAACCCCGTGGAAGCCGAAGACACCGCCAACTACTACTGCCAGCACAGCAGAG
AGCTGCCCTGGACATTTGGCCAGGGCACCAAGGTGGAAATCAAGCGAACTGTGGCTG
CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCT
GTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGG
ATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGG
ACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGA
GCTTCAACAGGGGAGAGTGT

Heavy chain (heavy chain 1) of BCMA arm: SEQ ID NO. 86
QVQLVQSGSELKKPGASVKVSCKASGYIFTNFGMNWVREAPGQGLEWMGWINTYTGEQ
IYADGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYFCARGEIYYGYDVGFVYWGQGTLVT
VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEMTK
NQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 87
CAGGTTCAGCTGGTGCAGTCTGGCAGCGAGCTGAAGAAACCTGGCGCCTCTGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACATCTTCACCAACTTCGGCATGAACTGGGTCCGAG
AGGCTCCTGGACAGGGACTCGAATGGATGGGCTGGATCAACACCTACACCGGCGAGC
AGATCTACGCCGATGGCTTCACAGGCAGATTCGTGTTCAGCCTGGACACCAGCGTCAG
CACAGCTTACCTGCAGATCAGCTCTCTGAAGGCCGAGGATACCGCCGTGTACTTCTGT
GCCAGAGGCGAGATCTACTACGGCTACGACGTGGGCTTTGTGTACTGGGGCCAGGGAA
CACTGGTCACCGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCC
TTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTA
CTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCAT
ACCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCTGAGCAGCGTGGTGACCG
TGCCTTCCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGCCCA
GCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTCCCTGCCCCCCTT
GCCCTGCCCCCGAGTTCGAGGGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAA
GGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGTC
CCAGGAGGACCCCGAGGTCCAGTTTAATTGGTACGTGGACGGCGTGGAAGTGCATAAC
GCCAAGACCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGTG
CTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCC
AACAAGGGCCTGGCCAGCAGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCC
ACGGGAGCCCCAGGTCTGCACCCTGCCACCTAGCCAAGAGGAGATGACCAAGAACCA
GGTGTCCCTGAGCTGTGCCGTGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGG
GAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCCTGTGCTGGACAGC
GACGGCAGCTTCTTCCTGGTTTCCAAGCTGACCGTGGACAAGTCCAGATGGCAGGAG
GGCAACGTCTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGA
AGTCCCTGAGCCTGAGCCTGGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 66
QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQEKPGQAPRGLIGGTNKRAPWT
PARFSGSLLGGKAALTITGAQAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVT
LFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSY
LSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

TABLE 10-continued

Nucleotide sequence: SEQ ID NO. 67
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTCCTGGCGGCACAGTGACC
CTGACCTGTAGATCTTCTACAGGCGCCGTGACCACCAGCAACTACGCTAATTGGGTGC
AGGAGAAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAAACAAGAGAGCC
CCTTGGACACCCGCCAGATTCTCTGGATCTCTGCTCGGCGGAAAGGCCGCTCTGACAA
TCACTGGTGCTCAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGTACAGCAA
CCTGTGGGTGTTCGGCGGAGGCACCAAACTGACAGTTCTGGGTCAGCCCAAGGCGGC
GCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACA
CTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGTGACAGTGGCCTGGAAGGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACA
ACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACA
GAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCC
CTACAGAATGTTCA

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 68
EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRKAPGKGLEWVGRIRSKYNNYA
TYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQE
EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 69
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGCCTGGCGGATCTCTGAGA
CTGTCTTGTGCCGCCAGCGGCTTCACCTTCAACACCTACGCTATGAACTGGGTCCGAA
AGGCCCCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCAAGTACAACAACT
ACGCCACCTACTACGCCGACAGCGTGAAGGACAGATTCACCATCAGCAGGGACGACA
GCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCGCCGTGT
ACTACTGTGTCAGACACGGCAACTTCGGCAACAGCTATGTGTCTTGGTTTGCCTACTGG
GGCCAGGGCACACTGGTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCC
CCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTGG
TGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCA
GCGGCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCTGAGCAG
CGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGA
CCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTC
CCTGCCCCCCTTGCCCTGCCCCCGAGTTCGAGGGCGGACCTAGCGTGTTCCTGTTCCC
CCCCAAGCCCAAGGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGTGGT
GGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTACGTGGACGGCGT
GGAAGTGCATAACGCCAAGACCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAG
AGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAA
GTGCAAGGTCTCCAACAAGGGCCTGGCCAGCAGCATCGAGAAGACCATCAGCAAGGC
CAAGGGCCAGCCACGGGAGCCCCAGGTCTACACCCTGCCACCTTGTCAAGAGGAGAT
GACCAAGAACCAGGTGTCCCTGTGGTGTCTGGTGAAAGGCTTCTATCCCAGCGATATC
GCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCT
GTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCAAGCTGACCGTGGACAAGTCCA
GATGGCAGGAGGGCAACGTCTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACC
ACTACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

BCMA × CD3 κλ006
κ light chain of BCMA arm: SEQ ID NO. 84
DIVLTQSPASLAVSPGQRATITCRASKSVTTSGYSYIHWYQKKPGQPPKLLIYLASDLEAGV
PARFSGSGSGTDFTLTINPVEAEDTANYYCQHSRELPWTFGQGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Nucleotide sequence: SEQ ID NO. 85
GACATCGTGCTGACACAGAGCCCTGCTTCTCTGGCTGTGTCTCCTGGCCAGAGAGCCA
CCATCACCTGTAGAGCCAGCAAGAGCGTGACCACCAGCGGCTACTCTTACATCCACTG
GTATCAGAAGAAGCCCGGCCAGCCTCCTAAGCTGCTGATCTACCTGGCCAGCGATCTG
GAAGCTGGCGTGCCAGCTAGATTTTCTGGCAGCGGCTCTGGCACCGACTTCACCCTGA
CAATCAACCCCGTGGAAGCCGAAGACACCGCCAACTACTACTGCCAGCACAGCAGAG
AGCTGCCCTGGACATTTGGCCAGGGCACCAAGGTGGAAATCAAGCGAACTGTGGCTG
CACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCT
GTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGG
ATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGG
ACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAAC
ACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGA
GCTTCAACAGGGGAGAGTGT

Heavy chain (heavy chain 1) of BCMA arm: SEQ ID NO. 86
QVQLVQSGSELKKPGASVKVSCKASGYIFTNFGMNWVREAPGQGLEWMGWINTYTGEQ
IYADGFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYFCARGEIYYGYDVGFVYWGQGTLVT
VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV

TABLE 10-continued

FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEMTK
NQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 87
CAGGTTCAGCTGGTGCAGTCTGGCAGCGAGCTGAAGAAACCTGGCGCCTCTGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACATCTTCACCAACTTCGGCATGAACTGGGTCCGAG
AGGCTCCTGGACAGGGACTCGAATGGATGGGCTGGATCAACACCTACACCGGCGAGC
AGATCTACGCCGATGGCTTCACAGGCAGATTCGTGTTCAGCCTGGACACCAGCGTCAG
CACAGCTTACCTGCAGATCAGCTCTCTGAAGGCCGAGGATACCGCCGTGTACTTCTGT
GCCAGAGGCGAGATCTACTACGGCTACGACGTGGGCTTTGTGTACTGGGGCCAGGGAA
CACTGGTCACCGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCC
TTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTA
CTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCAT
ACCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCTGAGCAGCGTGGTGACCG
TGCCTTCCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGCCCA
GCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTCCCTGCCCCCCTT
GCCCTGCCCCCGAGTTCGAGGGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAA
GGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGTC
CCAGGAGGACCCCGAGGTCCAGTTTAATTGGTACGTGGACGGCGTGGAAGTGCATAAC
GCCAAGACCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGTG
CTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCC
AACAAGGGCCTGGCCAGCAGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCC
ACGGGAGCCCCAGGTCTGCACCCTGCCACCTAGCCAAGAGGAGATGACCAAGAACCA
GGTGTCCCTGAGCTGTGCCGTGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGG
GAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGC
GACGGCAGCTTCTTCCTGGTTTCCAAGCTGACCGTGGACAAGTCCAGATGGCAGGAG
GGCAACGTCTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGA
AGTCCCTGAGCCTGAGCCTGGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 66
QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQEKPGQAPRGLIGGTNKRAPWT
PARFSGSLLGGKAALTITGAQAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVT
LFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSY
LSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Nucleotide sequence: SEQ ID NO. 67
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTCCTGGCGGCACAGTGACC
CTGACCTGTAGATCTTCTACAGGCGCCGTGACCACCAGCAACTACGCTAATTGGGTGC
AGGAGAAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAAACAAGAGAGCC
CCTTGGACACCCGCCAGATTCTCTGGATCTCTGCTCGGCGGAAAGGCCGCTCTGACAA
TCACTGGTGCTCAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGTACAGCAA
CCTGTGGGTGTTCGGCGGAGGCACCAAACTGACAGTTCTGGGTCAGCCCAAGGCGGC
GCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACA
CTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGTGACAGTGGCCTGGAAGGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACA
ACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACA
GAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCC
CTACAGAATGTTCA

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 68
EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRKAPGKGLEWVGRIRSKYNNYA
TYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQE
EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 69
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGCCTGGCGGATCTCTGAGA
CTGTCTTGTGCCGCCAGCGGCTTCACCTTCAACACCTACGCTATGAACTGGGTCCGAA
AGGCCCCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCAAGTACAACAACT
ACGCCACCTACTACGCCGACAGCGTGAAGGACAGATTCACCATCAGCAGGGACGACA
GCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCGCCGTGT
ACTACTGTGTCAGACACGGCAACTTCGGCAACAGCTATGTGTCTTGGTTTGCCTACTGG
GGCCAGGGCACACTGGTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCC
CCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTGG
TGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCA
GCGGCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCTGAGCAG
CGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGA
CCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTC
CCTGCCCCCCTTGCCCTGCCCCCGAGTTCGAGGGCGGACCTAGCGTGTTCCTGTTCCC
CCCCAAGCCCAAGGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGTGGT
GGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTACGTGGACGGCGT

TABLE 10-continued

GGAAGTGCATAACGCCAAGACCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAG
AGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAA
GTGCAAGGTCTCCAACAAGGGCCTGGCCAGCAGCATCGAGAAGACCATCAGCAAGGC
CAAGGGCCAGCCACGGGAGCCCCAGGTCTACACCCTGCCACCTTGTCAAGAGGAGAT
GACCAAGAACCAGGTGTCCCTGTGGTGTCTGGTGAAAGGCTTCTATCCCAGCGATATC
GCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCT
GTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCAAGCTGACCGTGGACAAGTCCA
GATGGCAGGAGGGCAACGTCTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACC
ACTACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

2. Expression and Purification of Anti-BCMA×CD3 κλ Bispecific Antibodies

[0267] The plasmids encoding the corresponding antibody fragments were mixed according to light chain (κ light chain) of BCMA arm: light chain (λ light chain) of CD3 arm: heavy chain (heavy chain 1) of BCMA arm: heavy chain (heavy chain 2) of CD3 arm=2:2:1:1 ratio. After mixing with 3 mg/mL PEI, co-transfecting of CHO-S cells, and culture in 500 mL CD CHO AGT medium (Gibco #12490-001) at 37° C. 5% CO_2 at 150 rpm, 4% CHO Feed C+supplement (Gibco #A25031-05) was added at transient day 2, 4 and 6, respectively. When the cell viability decreased to about 85%, the fermentation broth was harvested, filtered and purified by Protein A affinity chromatography, and the SEC-HPLC monomer content was close to or higher than 92%. The monomer content was further increased to above 98-99% by Capto S ImpAct ion exchange chromatography (Table 11).

TABLE 11

Purity of BCMA × CD3 κλ bispecific antibody

	HPLC-SEC (post Protein A)			HPLC-SEC (after cation exchange chromatography)		
HPLC detection	Mer	Monomer	Fragment	Mer	Monomer	Fragment
BCMA × CD3 κλ003	2.3%	94.4%	3.3%	1.8%	98.2%	0.0%
BCMA × CD3 κλ004	1.4%	95.2%	3.4%	1.0%	99.0%	0.0%
BCMA × CD3 κλ005	2.0%	91.9%	6.2%	1.6%	98.4%	0.0%
BCMA × CD3 κλ006	0.5%	96.4%	3.1%	0.6%	99.4%	0.0%

3. Binding Activity of BCMA×CD3 κλ Bi-Specific Antibodies

(1) Determination of Affinity of BCMA×CD3 κλ Bispecific Antibody to Antigen

[0268] 10 μg/mL human or cynomolgus monkey BCMA or CD3εγ recombinant antigen was bound to a CM5 chip (GE healthcare) by amino conjugating, while the amount of antigen bound was controlled to approximately 200 RU. After baseline plateau, gradient diluted antibodies (7 gradients of 2-fold dilutions from 10 μg/mL) were flowed through the chip at a flow rate of 30 μL/min for a binding time of 350 seconds and a dissociation time of 600 seconds. Kinetic constants were fitted using Biacore T200 evaluation software with a 1: 1 binding model. The results of the affinity determination are shown in Table 12.

TABLE 12

Affinities of BCMA × CD3κλ bispecific antibodies to antigens

KD(nM)	Human BCMA	Cynomolgus monkey BCMA	Human CD3εγ	Cynomolgus monkey CD3εγ
BCMA × CD3 κλ003	1.3	0.16	31	43
BCMA × CD3 κλ004	1.0	0.12	32	43
BCMA × CD3 κλ005	1.1	0.09	28	20
BCMA × CD3 κλ006	1.2	0.10	27	33

(2) Binding of BCMA×CD3 κλ Bispecific Antibody to BCMA+Cells

[0269] Logarithmically growing CHO-human BCMA stably transfected cells (CHO-hBCMA) and CHO-cynomolgus monkey BCMA stably transfected cells (CHO-cynoBCMA), and tumor cells NCI-H929 and RPMI-8226, respectively, were blocked and 100 μL of gradient diluted antibody (starting concentration 1800 nM, 3-fold dilution, 10 gradients) was added to each well and incubated for 60 min at 4° C. 50 μL/well Alexa Fluro647 labeled goat anti-human IgG Fc (1: 300 dilution) were added to the secondary antibody, incubated on ice for 20 min, added with 50 μL/well PI solution (1: 300) after washing once, incubated for 5 min, and flow cytometer was used to make detection. FIG. **20** shows that the BCMA×CD3 κλ bispecific antibody binds with high affinity to human, cynomolgus monkey BCMA stably transfected cells. FIG. **21** shows that the BCMA×CD3 κλ bispecific antibody binds with high affinity to BCMA+ tumor cells NCI-H929 and RPMI-8226. The binding constants EC_{50} of the BCMA×CD3 κλ bispecific antibody to cells are shown in Table 13.

TABLE 13

Binding of BCMA × CD3 κλ bispecific antibodies to BCMA stably transfected cells.

EC_{50}(nM)	Human BCMA-CHO	Cynomolgus monkey BCMA-CHO	NCI-H929	RPMI-8226
BCMA × CD3 κλ003	16	3	34	34
BCMA × CD3 κλ004	22	3	36	39
BCMA × CD3 κλ005	24	3	33	38
BCMA × CD3 κλ006	16	3	32	19
KLH × CD3	—	—	—	—

(3) Binding of BCMA×CD3 κλ Bispecific Antibody to Jurkat Cells

[0270] Jurkat cells in logarithmic growth phase were added with 200 μg/mL murine IgG (Jackson ImmunoResearch, 115-005-03) and incubated on ice for 30 minutes. The cells were adjusted to 5×105 cells/mL with 4% calf serum, 100 μL/well was added to 96-well U-plate, 300 g was centrifuged to removed the supernatant, 100 μL/well of gradient diluted antibody (initial concentration: 1800 nM, 3-fold dilution, 10 gradients) was added and incubated at 4° C. for 60 min. 50 μL/well Alexa Fluro647-labeled goat anti-human IgG Fc (1: 300 dilution) was added to the secondary antibody and incubated on ice for 20 min. 50 μL/well PI was added after washing once, incubated for 5 min, and detected with flow cytometer (BD C6). The results are shown in FIG. **22** and Table 14. The BCMA×CD3 κλ bispecific antibody binds human leukemia T-cell line Jurkat cells with moderate affinity.

(4) Binding of BCMA×CD3 κλ Bispecific Antibody to Peripheral Blood T-Cells

[0271] Fresh human peripheral blood was taken and PBMC was isolated by Ficoll. Paque Plu (GE, 17-1440-03). PBMC was adjusted to 5×10^5 cells/mL with 4% calf serum (Hyclone, SH30626.06), 100 μL/well was added to a 96-well U-plate, the supernatant was centrifuged off and 100 μL of gradient diluted antibody (with starting concentration of 1800 nM, 3-fold dilution, 10 gradients) was added to each well and incubated for 60 min at 4° C. 50 μL/well of Alexa Fluro647 labeled goat anti-human IgG Fc (1: 300 dilution) was added to the secondary antibody, with ice bath for 20 min, and 50 μL/well PI added after washing once, incubated for 5 min, and flow cytometer (BD C6) was used for detection. The control antibody REGN5458 was synthesized and prepared according to US20200024356. As shown in FIG. **23** and Table 14. The BCMA×CD3κλ bispecific antibody recognizes human peripheral blood CD4+T and CD8+ T-cells with an affinity of about 60-97 nM, which is weaker than the binding force of the BCMA antigen arm to the BCMA receptor, so that the bispecific antibody preferentially enriches into tumor cells.

TABLE 14

Binding of BCMA × CD3 κλ bispecific antibodies to Jurkat cells

EC_{50}(nM)	Jurkat	CD4 + T	CD8 + T
BCMA × CD3 κλ003	66	89	97
BCMA × CD3 κλ004	61	79	67
BCMA × CD3 κλ005	51	66	60
BCMA × CD3 κλ006	56	91	93
KLH × CD3	76	57	62

4. TDCC Mediated by BCMA×CD3 κλ Bispecific Antibody

[0272] Freshly isolated PBMC was mixed with target cells in logarithmic growth phase, NCI-H929 and RPMI-8226 cells, respectively, with effect/target cell=8: 1. 50 μL of gradient diluted antibody (antibody concentration from 66.7 nM, 10-fold dilution, 7 gradients) was added to each well and incubated for 24 h at 37° C. in 5% CO_2. At the end of the incubation, 50 μL of the supernatant was transferred to a new black elisa plate, 50 μL/well of LDH detection substrate was added, the reaction was stopped after 10 minutes and LDH release was detected. The remaining cells in the wells were washed twice with 4% calf blood, incubated with 100 μg/mL human IgG for 10 minutes, followed by T-cell activation detection antibodies (CD25-PE, CD4-APC, CD69-FITC and CD8-APC) and incubated on ice for 20 minutes. The supernatant was washed and discarded, 60 μL/well PI was added, incubated on ice for 5 minutes and detected by flow cytometry. FIGS. **24**A, **24**B show killing of NCI-H929 cells and activation of T-cells, respectively, by BCMA×CD3 κλ bispecific antibody. FIGS. **25**A, **25**B show killing of RPMI-8226 cells and activation of T-cells by CMA×CD3 κλ bispecific antibody, respectively. For tumor cells NCI-H929 and RPMI-8226 with different expression levels of BCMA, the BCMA×CD3 κλ bispecific antibody can mediate effective killing of T-cells, and the killing activity is equivalent to that of control antibody REGN5458.

5. Activation of T-Cell Activation Pathway by BCMA×CD3 κλ Bispecific Antibody

[0273] Logarithmically growing Jurkat-NFAT-luc reporter cells and BCMA-positive target cells RPMI-8226 were taken, centrifuged to discard the supernatant and resuspended to 2×10^6 cells/ml. 50 μl/well of the target cells were inoculated into a 96-well plate, the supernatant was discarded by centrifugation at 300 g for 5 minutes, and 50 μl/well of the Jurkat-NFAT-luc reporter cells were inoculated into a 96-well plate, and 501 of gradient diluted BCMA× CD3 κλ bispecific antibody or control antibody KLH×CD3 (with a starting concentration of 20 μg/ml, 10-fold dilution, 10 gradients) was added to each well, and incubated at 37° C. for 6 hours in 5% CO_2. After the incubation, 100 μL of detection reagent was added to each well according to ONE-Glo Luciferase Assay System instructions, allowed to stand at room temperature for 3 minutes, and detected on a microplate reader (Biotek Synergy HT). The detection results are shown in FIG. **26**. The BCMA×CD3κλ bispecific antibody can activate the NFAT signaling pathway of T-cells when RPMI-8226 tumor cells are used as target cells. In the absence of target cells, the NFAT signaling pathway is not activated.

6. Non-Specific Activation of PBMC by BCMA×CD3 κλ Bispecific Antibody

[0274] Freshly isolated PBMC was taken and 50 μL of gradient diluted antibody (with antibody concentration from 66.7 nM, 10-fold dilution, 7 gradients) was added to each well and incubated at 37° C. in 5% CO_2 for 24 hours. At the end of the incubation, 50 μL of the supernatant was transferred to a new black elisa plate, 50 μL/well of LDH detection substrate was added, the reaction was stopped after 10 minutes and LDH release was detected. The remaining cells in the wells were washed twice with 4% calf blood, incubated with 100 μg/mL human IgG for 10 minutes, followed by T-cell activation detection antibodies (CD25-PE, CD4-APC, CD69-FITC and CD8-APC) and incubated on ice for 20 minutes. The supernatant was washed and discarded, 60 μL/well PI was added, incubated on ice for 5 minutes and detected by flow cytometry. The results are shown in FIG. **27**. In the absence of target cells, the BCMA×CD3 κλ bispecific antibody had no activation of peripheral blood T-cells, comparable to the negative control KLH×CD3.

7. Binding of BCMA×CD3κλ Humanized Bispecific Antibody to Fc Receptor

[0275] 50 Mg/ml of His-Tag antibody was amino-conjugated to a CM5 chip to capture the His6-tagged FcγRI, $FcγRIIA_{H131}$ and $FcγRIIIA_{V158}$ recombinant proteins, respectively, with a capture time of 40 seconds and a flow rate of 10 μL/min. After baseline plateau, the gradient diluted antibody (with starting concentration of 37.5 μg/mL, 2-fold dilution) was flowed through the chip at a flow rate of 30 μL/min, with an association time of 120 seconds and a dissociation time of 200 seconds, and affinity constants were obtained by fitting with Biacore evaluation software. As can be seen from FIG. **28**, the BCMA×CD30, bispecific antibody did not bind to FcγRI, $FcγRIIA_{H131}$ and $FcγRIIIA_{V158}$; the wild-type IgG4 control antibody bound FcγRI with high affinity and weakly bound to $FcγRIIA_{H131}$.

8. Subcutaneous NCI-H929 Xenograft Tumor Model in Immunodeficient Mice

[0276] Six to eight-week-old female B-NGD mice (Bio-Tech Co. Ltd.) were subcutaneously inoculated with $2×10^6$ NCI-H929 cells (mixed with Matrigel 1: 1). When the tumors grew to 60 mm^3, they were randomly divided into dose group (3.0 mg/kg), dose group (0.6 mg/kg) and negative control group (KLH×CD3 3 mg/kg). Each mouse received $1×10^7$ PBMC cells via tail vein injection. Three days later, the first dose was administered to the mouse once every 5 days for a total of 2 doses. The tumor volume and body weight of the mice were monitored every 2 days. At the end of the experiment, the mice were killed by cervical dislocation and the tumors were collected and weighed. The results are shown in FIG. **29**. The in vivo efficacy of BCMA×CD3κλ bispecific antibody was dose-related. The tumor inhibition rates in 3.0 mg/kg group and 0.6 mg/kg group were 95% and 108% (BCMA×CD3κλ005) and 94% and 108% (BCMA×CD3κλ006), respectively. The tumor-bearing mice tolerated the foregoing doses well, without weight loss and other adverse reactions.

Example 4: Construction of GPC3×CD3 κλ Bispecific Antibodies Formed by Different Types of Light Chains

1. Construction of GPC3×CD3 κλ Bispecific Antibody

[0277] A GPC3 antibody containing a κ light chain and a humanized anti-CD3 antibody containing k light chain, with reference to Example 2, were used to construct a novel GPC3-CD3κλ humanized bispecific antibody having the native IgG configuration, while introduction in the GPC3 antigen arm and the CD3 arm is made of charge variants ($Vκ_{GPC3}$: $Gln_{43}Lys$; VH_{GPC3}: $Gln_{39}Glu$; $Vλ_{CD3}$: $Gln_{40}Glu$; VH_{CD3}: $Gln_{39}Lys$) (see Table 15 for sequence). The Fc portion of the bispecific antibody adopts the human IgG4 knob-into-hole structure to achieve heterodimer pairing, and through mutation of $Ser_{228}Pro$, $Leu_{235}Glu$, and $Pro_{329}Ala$, the hinge region remains stable and interaction with Fey receptor and Clq is reduced.

TABLE 15

GPC3 × CD3κλ humanized bispecific antibody

	light chain of CD20 arm	heavy chain of CD20 arm	light chain of CD20 arm	heavy chain of CD20 arm
GPC3 × CD3 κλ002	SEQ ID NO. 88	SEQ ID NO. 90	SEQ ID NO. 66	SEQ ID NO. 68
GPC3 × CD3 κλ003	SEQ ID NO. 92	SEQ ID NO. 94	SEQ ID NO. 66	SEQ ID NO. 68

GPC3 × CD3 κλ002:
κ light chain of GPC3 arm: SEQ ID NO. 88
DVVMTQSPLSLPVTPGEPASISCRSSQSIVHSNGNTYLEWYLKKPGQSPQLLIYKVSNRFSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVYFCLQVTHVPLTFGQGTKLEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Nucleotide sequence: SEQ ID NO. 89
GACGTGGTCATGACACAGAGCCCTCTGAGCCTGCCTGTGACACCTGGCGAACCTGCC
AGCATCAGCTGTAGAAGCAGCCAGAGCATCGTGCACAGCAACGGCAACACATACCTG
GAGTGGTATCTGAAGAAGCCCGGCCAGTCTCCTCAGCTGCTGATCTACAAGGTGTCCA
ACAGATTCAGCGGCGTGCCCGACAGATTCTCTGGCTCTGGATCTGGCACCGACTTCAC
CCTGAAGATCTCCAGAGTGGAAGCCGAGGACGTGGGCGTGTACTTCTGTCTCCAGGTC
ACACACGTGCCCCTGACATTTGGCCAGGGCACCAAGCTGGAAATCAAGCGAACTGTG
GCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGC
CTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAG

TABLE 15-continued

GTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGC
AAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAG
AAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGT

Heavy Chain (Heavy Chain 1) of GPC3 arm: SEQ ID NO. 90
QVQLVQSGAEVKKPGSSVKVSCKASGYTFADYEIHWVREAPGQGLEWMGAIHPGSGGTA
YAQKFQGRVTLTADESSTTAYMELSSLRSEDTAVYYCTRYYSFAYWGQGTLVTVSSASTK
GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEMTKNQVSLS
CAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCS
VMHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 91
CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCAGCAGCGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACACCTTCGCCGACTACGAGATCCACTGGGTCCGAG
AGGCTCCAGGACAGGGACTTGAATGGATGGGCGCTATCCATCCTGGCTCTGGCGGCAC
AGCTTACGCCCAGAAATTCCAGGGCAGAGTGACCCTGACCGCCGACGAGTCTAGCAC
CACCGCCTACATGGAACTGAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTG
CACCCGGTACTACAGCTTCGCCTACTGGGGACAGGGAACCCTGGTCACAGTCAGCTCT
GCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCTTGCAGCAGAAGCACCAGC
GAGAGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC
GTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCATACCTTCCCCGCCGTGCTCC
AGAGCAGCGGACTGTACTCCCTGAGCAGCGTGGTGACCGTGCCTTCCAGCAGCCTGG
GCACCAAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACACCAAGGTGGACA
AGAGAGTGGAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCGA
GGGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGC
AGAACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTC
CAGTTTAATTGGTACGTGGACGGCGTGGAAGTGCATAACGCCAAGACCAAGCCCAGA
GAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAG
GACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGGCCTGGCCAGC
AGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTCTGC
ACCCTGCCACCTAGCCAAGAGGAGATGACCAAGAACCAGGTGTCCCTGAGCTGTGCC
GTGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG
AGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGCTTCTTCCTGGT
TTCCAAGCTGACCGTGGACAAGTCCAGATGGCAGGAGGGCAACGTCTTCAGCTGCTC
CGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGAGCCTGAGCCT
GGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 66
QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQEKPGQAPRGLIGGTNKRAPWT
PARFSGSLLGGKAALTITGAQAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVT
LFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSY
LSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Nucleotide sequence: SEQ ID NO. 67
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTCCTGGCGGCACAGTGACC
CTGACCTGTAGATCTTCTACAGGCGCCGTGACCACCAGCAACTACGCTAATTGGGTGC
AGGAGAAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAAACAAGAGAGCC
CCTTGGACACCCGCCAGATTCTCTGGATCTCTGCTCGGCGGAAAGGCCGCTCTGACAA
TCACTGGTGCTCAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGTACAGCAA
CCTGTGGGTGTTCGGCGGAGGCACCAAACTGACAGTTCTGGGTCAGCCCAAGGCGGC
GCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACA
CTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGTGACAGTGGCCTGGAAGGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACA
ACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACA
GAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCC
CTACAGAATGTTCA

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 68
EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRKAPGKGLEWVGRIRSKYNNYA
TYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQE
EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 69
GAGGTGCAGCTGGTTGAATCTGGCGGAGGACTGGTTCAGCCTGGCGGATCTCTGAGA
CTGTCTTGTGCCGCCAGCGGCTTCACCTTCAACACCTACGCTATGAACTGGGTCCGAA
AGGCCCCTGGCAAAGGACTGGAATGGGTGGGAAGAATCAGGTCCAAGTACAACAACT
ACGCCACCTACTACGCCGACAGCGTGAAGGACAGATTCACCATCAGCAGGGACGACA
GCAAGAACAGCCTGTACCTGCAGATGAACAGCCTGAAAACCGAGGACACCGCCGTGT

TABLE 15-continued

ACTACTGTGTCAGACACGGCAACTTCGGCAACAGCTATGTGTCTTGGTTTGCCTACTGG
GGCCAGGGCACACTGGTCACAGTTAGCTCTGCTAGCACCAAGGGCCCCAGCGTGTTCC
CCCTGGCCCCTTGCAGCAGAAGCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTGG
TGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGCGCTCTGACCA
GCGGCGTGCATACCTTCCCCGCCGTGCTCCAGAGCAGCGGACTGTACTCCCTGAGCAG
CGTGGTGACCGTGCCTTCCAGCAGCCTGGGCACCAAGACCTACACCTGCAACGTGGA
CCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGAGCAAGTACGGCCCTC
CCTGCCCCCCTTGCCCTGCCCCCGAGTTCGAGGGCGGACCTAGCGTGTTCCTGTTCCC
CCCCAAGCCCAAGGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGCGTGGT
GGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTTAATTGGTACGTGGACGGCGT
GGAAGTGCATAACGCCAAGACCAAGCCCAGAGAGGAGCAGTTCAACAGCACCTACAG
AGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAA
GTGCAAGGTCTCCAACAAGGGCCTGGCCAGCAGCATCGAGAAGACCATCAGCAAGGC
CAAGGGCCAGCCACGGGAGCCCCAGGTCTACACCCTGCCACCTTGTCAAGAGGAGAT
GACCAAGAACCAGGTGTCCCTGTGGTGTCTGGTGAAAGGCTTCTATCCCAGCGATATC
GCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCT
GTGCTGGACAGCGACGGCAGCTTCTTCCTGTACTCCAAGCTGACCGTGGACAAGTCCA
GATGGCAGGAGGGCAACGTCTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAACC
ACTACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

GPC3 × CD3 κλ003:
κ light chain of GPC3 arm: SEQ ID NO. 92
DVVMTQSPLSLPVTPGEPASISCRSSQSIVHSNGNTYLEWYLKKPGQSPQLLIYKVSNRFSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVYFCLQVTHVPLTFGQGTKLEIKRTVAAPSVFIFP
PSDKKLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Nucleotide sequence SEQ ID NO. 93
GACGTGGTCATGACACAGAGCCCTCTGAGCCTGCCTGTGACACCTGGCGAACCTGCC
AGCATCAGCTGTAGAAGCAGCCAGAGCATCGTGCACAGCAACGGCAACACATACCTG
GAGTGGTATCTGAAGAAGCCCGGCCAGTCTCCTCAGCTGCTGATCTACAAGGTGTCCA
ACAGATTCAGCGGCGTGCCCGACAGATTCTCTGGCTCTGGATCTGGCACCGACTTCAC
CCTGAAGATCTCCAGAGTGGAAGCCGAGGACGTGGGCGTGTACTTCTGTCTCCAGGTC
ACACACGTGCCCCTGACATTTGGCCAGGGCACCAAGCTGGAAATCAAGCGAACTGTG
GCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATAAGAAATTGAAATCTGGAACTGC
CTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAG
GTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGC
AAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAG
AAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACA
AAGAGCTTCAACAGGGGAGAGTGT

Heavy Chain (Heavy Chain 1) of GPC3 arm: SEQ ID NO. 94
QVQLVQSGAEVKKPGSSVKVSCKASGYTFADYEIHWVREAPGQGLEWMGAIHPGSGGTA
YAQKFQGRVTLTADESSTTAYMELSSLRSEDTAVYYCTRYYSFAYWGQGTLVTVSSASTK
GPSVFPLAPCSRSTSESTAALGCLVEDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTKTYTCNVDHKPSNTKVDERVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVCTLPPSQEEMTKNQVSLSC
AVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQEGNVFSCSV
MHEALHNHYTQKSLSLSLGK

Nucleotide sequence: SEQ ID NO. 95
CAGGTTCAGCTGGTTCAGTCTGGCGCCGAAGTGAAGAAACCTGGCAGCAGCGTGAAG
GTGTCCTGCAAGGCTAGCGGCTACACCTTCGCCGACTACGAGATCCACTGGGTCCGAG
AGGCTCCAGGACAGGGACTTGAATGGATGGGCGCTATCCATCCTGGCTCTGGCGGCAC
AGCTTACGCCCAGAAATTCCAGGGCAGAGTGACCCTGACCGCCGACGAGTCTAGCAC
CACCGCCTACATGGAACTGAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTG
CACCCGGTACTACAGCTTCGCCTACTGGGGACAGGGAACCCTGGTCACAGTCAGCTCT
GCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCTTGCAGCAGAAGCACCAGC
GAGAGCACAGCCGCCCTGGGCTGCCTGGTGGAGGACTACTTCCCCGAGCCCGTGACC
GTGTCCTGGAACAGCGGCGCTCTGACCAGCGGCGTGCATACCTTCCCCGCCGTGCTCC
AGAGCAGCGGACTGTACTCCCTGAGCAGCGTGGTGACCGTGCCTTCCAGCAGCCTGG
GCACCAAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACACCAAGGTGGACG
AGAGAGTGGAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCGA
AGGCGGACCTAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGC
AGAACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTC
CAGTTTAATTGGTACGTGGACGGCGTGGAAGTGCATAACGCCAAGACCAAGCCCAGA

TABLE 15-continued

GAGGAGCAGTTCAACAGCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAG
GACTGGCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGGCCTGGCCAGC
AGCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTCTGC
ACCCTGCCACCTAGCCAAGAGGAGATGACCAAGAACCAGGTGTCCCTGAGCTGTGCC
GTGAAAGGCTTCTATCCCAGCGATATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG
AGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGCTTCTTCCTGGT
TTCCAAGCTGACCGTGGACAAGTCCAGATGGCAGGAGGGCAACGTCTTCAGCTGCTC
CGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGAGCCTGAGCCT
GGGCAAG

λ light chain of CD3 arm: SEQ ID NO. 66
QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQEKPGQAPRGLIGGTNKRAPWT
PARFSGSLLGGKAALTITGAQAEDEAEYYCVLWYSNLWVFGGGTKLTVLGQPKAAPSVT
LFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSY
LSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Nucleotide sequence: SEQ ID NO. 67
CAGGCTGTGGTCACACAAGAGCCTAGCCTGACAGTGTCTCCTGGCGGCACAGTGACC
CTGACCTGTAGATCTTCTACAGGCGCCGTGACCACCAGCAACTACGCTAATTGGGTGC
AGGAGAAGCCCGGCCAGGCTCCTAGAGGACTGATCGGCGGAACAAACAAGAGAGCC
CCTTGGACACCCGCCAGATTCTCTGGATCTCTGCTCGGCGGAAAGGCCGCTCTGACAA
TCACTGGTGCTCAGGCTGAGGACGAGGCCGAGTACTATTGTGTGCTGTGGTACAGCAA
CCTGTGGGTGTTCGGCGGAGGCACCAAACTGACAGTTCTGGGTCAGCCCAAGGCGGC
GCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACA
CTGGTGTGTCTCATAAGTGACTTCTATCCGGGAGCCGTGACAGTGGCCTGGAAGGCAG
ATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACA
ACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACA
GAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCC
CTACAGAATGTTCA

Heavy chain (heavy chain 2) of CD3 arm: SEQ ID NO. 68
EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRKAPGKGLEWVGRIRSKYNNYA
TYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLASSIEKTISKAKGQPREPQVYTLPPCQE
EMTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
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Nucleotide sequence: SEQ ID NO. 69
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ACTACACCCAGAAGTCCCTGAGCCTGAGCCTGGGCAAG

[0278] The plasmids encoding the corresponding antibody fragments were prepared according to the light chain (κ light chain) of GPC3 arm: light chain (λ light chain) of CD3 arm: heavy chain (heavy chain 1) of GPC3 arm: heavy chain (heavy chain 2) of CD3 arm=2:2:1:1 ratio, after mixing with 3 mg/mL PEI, co-transfecting of CHO-S cells, culture in 500 mL CD CHO AGT medium (Gibco #12490-001) at 37° C. 5% CO_2 at 150 rpm, 4% CHO Feed C+supplement (Gibco #A25031-05) was added at transient day 2, 4 and 6, respectively. When the cell viability decreased to about 85%, the fermentation broth was harvested, filtered and purified by Protein A affinity chromatography, and the SEC-HPLC monomer content was higher than 92%. The monomer content was further increased to above 99.5% by Butyl HP hydrophobic chromatography and Capto Q anion chromatography (Table 16).

TABLE 16

Purification of humanized GPC3-CD3 bispecific antibody

	HPLC-SEC (post Protein A)			HPLC-SEC (after anion chromatography)		
HPLC detection	Mer	Monomer	Fragment	Mer	Monomer	Fragment
GPC3 × CD3 κλ002	2.6%	94.2%	3.1%	0.0%	100.0%	0.0%
GPC3 × CD3 κλ003	2.2%	93.2%	4.5%	0.1%	99.5%	0.4%

2. Binding of GPC3×CD3 κλ Bispecific Antibody to GPC3 Stably Transfected Cells

[0279] CHO-human GPC3, CHO-Cynomolgus monkey GPC3 stably transfected cells or human hepatocellular carcinoma HepG2 tumor cells in logarithmic growth phase were taken. After blocking, the cells were adjusted to 5×10^5 cells/ml, and 100 μl/well cell suspension was added to 96-well U-shaped plate and centrifuged at 300 g for 5 min. The supernatant was discarded, 100 μL of gradient diluted antibody (with a starting concentration of 1800 nM, 3-fold dilution, 10 gradients) was added to each well, and incubated at 4° C. for 60 min. 50 μL/well Alexa Fluro647 labeled goat anti-human IgG Fc (1: 300 dilution) were added to the secondary antibody, incubated on ice for 20 min, added with 50 μL/well PI solution (1: 300) after washing once, incubated for 5 min, and flow cytometer was used to make detection. The results are shown in FIGS. **30-31** and Table 17. The GPC3×CD3 κλ bispecific antibody binds to GPC3+ cells with high affinity.

TABLE 17

Binding ofGPC3 × CD3 κλ bispecific antibodies to GPC3 + cells

EC_{50}	Human GPC3-CHO	Cynomolgus monkey GPC3-CHO	HepG2
GPC3 × CD3 κλ002	2.8 nM	3.0 nM	2.1 nM
GPC3 × CD3 κλ003	2.9 nM	3.0 nM	2.5 nM
KLH × CD3	Not combined	Not combined	Not combined

3. Binding of GPC3×CD3 κλ Bispecific Antibody to Jurkat Cells

[0280] Jurkat cells in logarithmic growth phase were added with 200 μg/mL murine IgG (Jackson ImmunoResearch, 115-005-03) and incubated on ice for 30 minutes. The cells were adjusted to 5×10^5 cells/mL with 4% calf serum, 100 μL/well was added to 96-well U-plate, 300 g was centrifuged to removed the supernatant, 100 μL/well of gradient diluted antibody (initial concentration: 1800 nM, 3-fold dilution, 10 gradients) was added and incubated at 4° C. for 60 min. 50 μL/well Alexa Fluro647-labeled goat anti-human IgG Fc (1: 300 dilution) was added to the secondary antibody and incubated on ice for 20 min. 50 μL/well PI was added after washing once, incubated for 5 min, and detected with flow cytometer (BD C6). As shown in FIG. **32** and Table 18, the GPC3×CD3 κλ bispecific antibody binds with moderate affinity to human leukemia T-cell line Jurkat cells with an EC_{50} of about 20-40 nM.

4. Binding of GPC3×CD3 κλ Bispecific Antibody to Peripheral Blood T-Cells

[0281] Fresh human or cynomolgus monkey peripheral blood was taken and PBMC was isolated by Ficoll. Paque Plus (GE, 17-1440-03). PBMC was adjusted to 5×10^5 cells/mL with 4% calf serum (Hyclone, SH30626.06), 100 μL/well was added to a 96-well U-plate, the supernatant was centrifuged off and 100 μL of gradient diluted antibody (with starting concentration of 1800 nM, 3-fold dilution, 10 gradients) was added to each well and incubated for 60 min at 4° C. 50 μL/well Alexa Fluro647 labeled goat anti-human IgG Fc (1: 300 dilution) was added to secondary antibody, with ice bath for 20 min. 50 μL/well PI was added after washing once and incubated for 5 min, and flow cytometer (BD Celesta) is used to make detection. The results are shown in FIG. **33** and Table 18. The GPC3×CD3 κλ bispecific antibody binds human peripheral blood T-cells with low affinity.

TABLE 18

Binding of GPC3 × CD3 κλ bispecific antibodies to T-cells

EC_{50}	Jurkat	CD4 + T	CD8 + T
GPC3 × CD3 κλ002	36 nM	65 nM	65 nM
GPC3 × CD3 κλ003	26 nM	56 nM	69 nM
KLH × CD3	27 nM	77 nM	84 nM

5. TDCC Mediated by GPC3×CD3 κλ Bispecific Antibody

[0282] Freshly isolated PBMC was mixed with target cells in logarithmic growth phase, hepG2 cells, respectively, at an effector/target cell ratio of 10:1. 50 μL of gradient diluted antibody (with antibody concentration from 66.7 nM, 10-fold dilution, 7 gradients) was added to each well and incubated for 24 h at 37° C. in 5% CO_2. At the end of the incubation, 50 μL of the supernatant was transferred to a new black ELISA plate, 50 μL/well of LDH detection substrate was added, the reaction was stopped after 10 minutes and LDH release was detected. The remaining cells in the wells were washed twice with 4% calf blood, incubated with 100 μg/mL human IgG for 10 minutes, followed by T-cell activation detection antibodies (CD25-BV421, CD4-FITC, CD69-BV605 and CD8-APC) and incubated on ice for 20 minutes. The supernatant was washed and discarded, 60 μL/well PI was added, incubated on ice for 5 minutes and detected by flow cytometry. FIGS. **34**A and **34**B show killing of HepG2 cells and activation of T-cells, respectively, by the GPC3×CD3 κλ bispecific antibody.

6. Activation of T-Cell Activation Pathway by GPC3×CD3 κλ Bispecific Antibody

[0283] Target cells CHO-human GPC3 in logarithmic growth phase were harvested, centrifuged, the supernatant discarded and resuspended to 2×10^5 cells/ml. 50l/well of target cells were seeded into 96-well plates and incubated overnight at 37° C. in 5% CO_2. The Jurkat-NFAT-luc reporter cells in logarithmic growth phase were taken and performed with centrifugation at 300 g for 5 min. The supernatant was discarded, and it resuspended to 4×10^6 cells/ml. The 96-well plate was taken out, the supernatant, inoculate Jurkat-NFAT-luc reporter cells were 4×10^6 into the 96-well plate at 25 μL/well and added with 25 μL of gradient diluted GPC3×CD3 κλ bispecific antibody or control antibody KLH×CD3 (with an initial concentration of 20 μg/ml, 3-fold dilution, 10 gradients) into each well, with was incubated at 37° C. for 6 h. After the incubation, 100 μL of detection reagent was added to each well according to ONE-Glo Luciferase Assay System instructions for detection in a microplate reader (MD SpectraMax i 3x). The detection results are shown in FIG. **35**. The GPC3×CD3κλ bispecific antibody can activate the NFAT signaling pathway of T-cell when CHO-human GPC3 is used as the target cell.

7. Non-Specific Activation of GPC3×CD3κλ Bispecific Antibody PBMC

[0284] Freshly isolated PBMC was added with 100 μL of antibody (10 μg/mL) and incubated at 37° C. in 5% CO_2 for 24 hours. The cells in the wells were washed twice with 4% calf blood, incubated with 100 μg/mL human IgG for 10 minutes, followed by T-cell activation detection antibodies (CD25-BV421, CD4-FITC, CD69-BV605 and CD8-APC) and incubated on ice for 20 minutes. The supernatant was washed and discarded, 60 μL/well PI was added, incubated on ice for 5 minutes and detected by flow cytometry. The positive control antibody ERY974 was prepared according to US20170267783. The results are shown in FIG. **36**. In the absence of target cells, GPC3×CD3 κλ bispecific antibody had no activation of peripheral blood T-cells, comparable to the negative control KLH×CD3.

8. Immune Reconstitution of Subcutaneous HepG2 Xenograft Model in Mice

[0285] Six to eight-week-old female B-NGD mice (Bio-Tech Co. Ltd.) were subcutaneously inoculated with HepG2 cells (7×10^6/mouse). When the tumors grew to 60-100 mm^3, they were randomly divided into high dose group (3.0 mg/kg), medium dose group (1.0 mg/kg), low dose group (0.3 mg/kg), positive control group (ERY974) and negative control group (KLH×CD3). Each mouse was injected intravenously with 1×10^7 PBMC cells via the tail vein. Three days later, the first dose was given to the mouse once every 5 days for a total of 2 doses. The tumor volume and body weight of the mice were monitored. At the end of the experiment, the mice were killed by cervical dislocation and the tumors were collected and weighed. The results are shown in FIG. **37**. The in vivo efficacy of GPC3×CD3 κλ bispecific antibody was dose-related, and the tumor inhibition rates (low-dose to high-dose) were: 76.7%, 81.3% and 95.9%. The tumor-bearing mice tolerated the foregoing doses well, without weight loss and other adverse reactions.

9. CD3 Humanized Murine Hepa1-6/Human GPC3 Xenograft Model

[0286] Six-week-old female C57/BL6-hCD3 mice (Biotech Bio-tech Co. Ltd.) were selected and inoculated with Hepa1-6/human GPC3 (6×106/mouse) subcutaneously. When the tumor volume reached 60-100 mm3, the mice were randomly divided into groups. The dose was set as 10 mg/mL in high dose group, 3 mg/mL in medium dose group low dose group 1 mg/mL, positive control group ERY974 and negative control group KLH×CD3 10 mg/kg. The dosing interval was once every 3 days for a total of 3 doses. The tumor volume and body weight of the mice were monitored. At the end of the experiment, the mice were killed by cervical dislocation and the tumors were collected and weighed. The results are shown in FIG. **38**. The GPC3×CD3κλ bispecific antibody significantly mediated immune cells to kill tumor cells and reduce tumor-bearing volume. Its 10 mg/kg dose was comparable to ERY974.

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Trp Phe Lys Asp Gly Lys Met Ile Gly Phe Leu Thr Glu Asp Lys Lys
        35                  40                  45

Lys Trp Asn Leu Gly Ser Asn Ala Lys Asp Pro Arg Gly Met Tyr Gln
    50                  55                  60

Cys Lys Gly Ser Gln Asn Lys Ser Lys Pro Leu Gln Val Tyr Tyr Arg
65                  70                  75                  80
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Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            100                 105                 110

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        115                 120                 125

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    130                 135                 140

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
145                 150                 155                 160

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
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Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile Glu
            180                 185                 190

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
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Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
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Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
225                 230                 235                 240

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
                245                 250                 255

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
            260                 265                 270

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        275                 280                 285

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Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys Asn Ile Gly Gly Asp
        35                  40                  45

Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp His Leu Ser Leu Lys
    50                  55                  60

Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr Val Cys Tyr Pro Arg
65                  70                  75                  80

Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu Tyr Leu Arg Ala Arg
                85                  90                  95

Val Cys Glu Asn Cys Met Glu Met Asp Ala Pro Glu Ala Ala Gly Gly
            100                 105                 110

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
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Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
145                 150                 155                 160

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                165                 170                 175

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            180                 185                 190

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile Glu
        195                 200                 205

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    210                 215                 220

Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
225                 230                 235                 240

Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                245                 250                 255

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            260                 265                 270

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        275                 280                 285

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    290                 295                 300

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
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Gly Lys Gly Ser Gly Leu Asn Asp Ile Phe Glu Ala Gln Lys Ile Glu
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Trp His Glu


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Gly Ser Val Leu Leu Thr Cys His Val Lys Asn Thr Asn Ile Thr Trp
            20                  25                  30

Phe Lys Glu Gly Lys Met Ile Asp Ile Leu Thr Ala His Lys Asn Lys
        35                  40                  45

Trp Asn Leu Gly Ser Asn Thr Lys Asp Pro Arg Gly Val Tyr Gln Cys
    50                  55                  60

Lys Gly Ser Lys Asp Lys Ser Lys Thr Leu Gln Val Tyr Tyr Arg Met
65                  70                  75                  80

Cys Gln Asn Cys Ile Glu Leu Asn Ala Pro Glu Ala Ala Gly Gly Pro
                85                  90                  95

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
            100                 105                 110

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
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Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
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Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Ser Ile Glu Lys
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Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
        195                 200                 205

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser
    210                 215                 220

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
225                 230                 235                 240

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
                245                 250                 255

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
            260                 265                 270

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
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Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
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Lys
305


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Gly Ser Glu Ala Gln Trp Gln His Asn Gly Lys Asn Lys Glu Asp Ser
        35                  40                  45

Gly Asp Arg Leu Phe Leu Pro Glu Phe Ser Glu Met Glu Gln Ser Gly
    50                  55                  60

Tyr Tyr Val Cys Tyr Pro Arg Gly Ser Asn Pro Glu Asp Ala Ser His
65                  70                  75                  80

His Leu Tyr Leu Lys Ala Arg Val Cys Glu Asn Cys Met Glu Met Asp
                85                  90                  95

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
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Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
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Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
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Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu
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Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro
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Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
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Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            260                 265                 270

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        275                 280                 285

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
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Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Ala
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cccgccagat tctctggatc tctgctcggc ggaaaggccg ctctgacact ttctggtgct    240

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Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Ala
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Leu Ile Gly Gly Thr Asn Lys Glu Ala Pro Trp Thr Pro Ala Arg Phe
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Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Ala
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<400> SEQUENCE: 16

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Glu Ser Ser Asp Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Glu Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Ala
65 70 75 80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 17
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

caggctgtgg tcacacaaga gcctagcctg acagtgtctc ctggcggcac agtgaccctg 60

acctgtgagt cttctgacgg cgccgtgacc accagcaact acgctaattg ggtgcaggag 120

aagcccggcc aggctcctag aggactgatc ggcggaacaa acaaggaggc cccttggaca 180

cccgccagat tctctggatc tctgctcggc ggaaaggccg ctctgacact ttctggtgct 240

cagcctgagg acgaggccga gtactattgt gccctgtggt acagcaacct gtgggtgttc 300

ggcggaggca ccaaactgac agttctg 327

<210> SEQ ID NO 18
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

-continued

Gln Ala Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 19
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

caggctgtgg tcacacaaga gcctagcctg acagtgtctc ctggcggcac agtgaccctg 60

acctgtagat cttctacagg cgccgtgacc accagcaact acgctaattg ggtgcaggag 120

aagcccggcc aggctcctag aggactgatc ggcggaacaa acaagagagc cccttggaca 180

cccgccagat tctctggatc tctgctcggc ggaaaggccg ctctgacaat cactggtgct 240

caggctgagg acgaggccga gtactattgt gtgctgtggt acagcaacct gtgggtgttc 300

ggcggaggca ccaaactgac agttctg 327

<210> SEQ ID NO 20
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Tyr Gly Thr Asn Lys Arg Ala Pro
1 5

<210> SEQ ID NO 21
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Val Leu Trp Tyr Ser Asn Leu Trp Val
1 5

<210> SEQ ID NO 22
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Phe Gln Glu Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Tyr Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Ala
65 70 75 80

Gln Ala Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

-continued

<210> SEQ ID NO 23
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

caggctgtgg tcacacaaga gcctagcctg acagtgtctc ctggcggcac agtgaccctg 60

acctgtagat cttctacagg cgccgtgacc accagcaact acgctaattg gttccaggag 120

aagcccggcc aggctcctag aggactgatc tacggaacaa acaagagagc cccttggaca 180

cccgccagat tctctggatc tctgctcggc ggaaaggccg ctctgacact ttctggtgct 240

caggctgagg acgaggccga gtactattgt gtcctgtggt acagcaacct gtgggtgttc 300

ggcggaggca ccaaactgac agttctg 327

<210> SEQ ID NO 24
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 25
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg 60

tcttgtgccg ccagcggctt caccttcaac acctacgcta tgaactgggt ccgacaggcc 120

cctggcaaag gactggaatg ggtgtccaga atcaggtcca agtacaacaa ctacgccacc 180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgagagcc gaggacaccg ccgtgtacta ctgtgtcaga 300

cacggcaact tcggcaacag ctatgtgtct tggtttgcct actggggcca gggcacactg 360

gtcacagtta gctct 375

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<210> SEQ ID NO 26
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Asn Thr Tyr Ala Met Asn
1 5

<210> SEQ ID NO 27
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val
1 5 10 15

Lys Asp

<210> SEQ ID NO 28
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr
1 5 10

<210> SEQ ID NO 29
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 30
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg 60

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tcttgtgccg ccagcggctt caccttctcc acctacgcta tgaactgggt ccgaaaggcc 120

cctggcaaag gactggaatg ggtgtccaga atcaggtcca agtacaacaa ctacgccacc 180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgagagcc gaggacaccg ccgtgtacta ctgtgtcaga 300

cacggcaact tcggcaacag ctatgtgtct tggtttgcct actggggcca gggcacactg 360

gtcacagtta gctct 375

<210> SEQ ID NO 31
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Ser Thr Tyr Ala Met Asn
1 5

<210> SEQ ID NO 32
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Glu Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 33
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg 60

tcttgtgccg ccagcggctt caccttctcc acctacgcta tgaactgggt ccgaaaggcc 120

cctggcaaag gactggaatg ggtgtccaga atcaggtcca agtacaacaa ctacgccacc 180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgagagcc gaggacaccg ccgtgtacta ctgtgtcaga 300

cacggcaact tcggcgagag ctatgtgtct tggtttgcct actggggcca gggcacactg 360

gtcacagtta gctct 375

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<210> SEQ ID NO 34
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

His Gly Asn Phe Gly Glu Ser Tyr Val Ser Trp Phe Ala Tyr
1 5 10

<210> SEQ ID NO 35
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20 25 30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
        35 40 45

Ser Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Gln Ser Tyr Val Ser Trp Phe
            100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115 120 125

<210> SEQ ID NO 36
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg 60

tcttgtgccg ccagcggctt caccttctcc acctacgcta tgaactgggt ccgaaaggcc 120

cctggcaaag gactggaatg ggtgtccaga atcaggtcca agtacaacaa ctacgccacc 180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgagagcc gaggacaccg ccgtgtacta ctgtgtcaga 300

cacggcaact tcggccagag ctatgtgtct tggtttgcct actggggcca gggcacactg 360

gtcacagtta gctct 375

<210> SEQ ID NO 37
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

His Gly Asn Phe Gly Gln Ser Tyr Val Ser Trp Phe Ala Tyr
1 5 10

-continued

<210> SEQ ID NO 38
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asp Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 39
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg 60

tcttgtgccg ccagcggctt caccttctcc acctacgcta tgaactgggt ccgaaaggcc 120

cctggcaaag gactggaatg ggtgtccaga atcaggtcca agtacaacaa ctacgccacc 180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgagagcc gaggacaccg ccgtgtacta ctgtgtcaga 300

cacggcaact tcggcgacag ctatgtgtct tggtttgcct actggggcca gggcacactg 360

gtcacagtta gctct 375

<210> SEQ ID NO 40
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

His Gly Asn Phe Gly Asp Ser Tyr Val Ser Trp Phe Ala Tyr
1 5 10

<210> SEQ ID NO 41
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20                  25                  30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Thr Ser Tyr Val Ser Trp Phe
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210> SEQ ID NO 42
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg     60

tcttgtgccg ccagcggctt caccttctcc acctacgcta tgaactgggt ccgaaaggcc    120

cctggcaaag gactggaatg ggtgtccaga atcaggtcca agtacaacaa ctacgccacc    180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacacc    240

ctgtacctgc agatgaacag cctgagagcc gaggacaccg ccgtgtacta ctgtgtcaga    300

cacggcaact tcggcaccag ctatgtgtct tggtttgcct actggggcca gggcacactg    360

gtcacagtta gctct                                                     375


<210> SEQ ID NO 43
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

His Gly Asn Phe Gly Thr Ser Tyr Val Ser Trp Phe Ala Tyr
1               5                   10


<210> SEQ ID NO 44
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60

Ser Val Glu Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
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65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 45
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg 60

tcttgtgccg ccagcggctt caccttctcc gactacgcta tgaactgggt ccgaaaggcc 120

cctggcaaag gactggaatg ggtgtccaga atcaggtcca agtacaacaa ctacgccacc 180

tactacgccg acagcgtgga ggacagattc accatcagca gggacgacag caagaacacc 240

ctgtacctgc agatgaacag cctgagagcc gaggacaccg ccgtgtacta ctgtgtcaga 300

cacggcaact tcggcaacag ctatgtgtct tggtttgcct actggggcca gggcacactg 360

gtcacagtta gctct 375

<210> SEQ ID NO 46
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Ser Asp Tyr Ala Met Asn
1 5

<210> SEQ ID NO 47
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val
1 5 10 15

Glu Asp

<210> SEQ ID NO 48
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

-continued

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 49
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg 60

tcttgtgccg ccagcggctt caccttcaac acctacgcta tgaactgggt ccgaaaggcc 120

cctggcaaag gactggaatg ggtgggaaga atcaggtcca agtacaacaa ctacgccacc 180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacagc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgtgccaga 300

cacggcaact tcggcaacag ctatgtgtct tggtttgcct actggggcca gggcacactg 360

gtcacagtta gctct 375

<210> SEQ ID NO 50
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 51
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg 60

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tcttgtgccg ccagcggctt caccttcaac acctacgcta tgaactgggt ccgaaaggcc 120

cctggcaaag gactggaatg ggtgggaaga atcaggtcca agtacaacaa ctacgccacc 180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacagc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgtgtcaga 300

cacggcaact tcggcaacag ctatgtgtct tggtttgcct actggggcca gggcacactg 360

gtcacagtta gctct 375

<210> SEQ ID NO 52
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 53
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg 60

tcttgtgccg ccagcggctt caccttcaac acctacgcta tgaactgggt ccgaaaggcc 120

cctggcaaag gactggaatg ggtggccaga atcaggtcca agtacaacaa ctacgccacc 180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacagc 240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgtgtcaga 300

cacggcaact tcggcaacag ctatgtgtct tggtttgcct actggggcca gggcacactg 360

gtcacagtta gctct 375

<210> SEQ ID NO 54
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly

-continued

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1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Ile
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> SEQ ID NO 55
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

```
gagatcgtgc tgacacagag ccctggcaca ctgtcactgt ctccaggcga gagagccaca     60

ctgagctgta gagccagcca gagcgtgtcc tcttacctgg cctggtatca gcagaagcct    120

ggacaggctc ccagactgct gatctacgac gccagcaaca gagccacagg catccccgat    180

agattcagcg gctctggctc tggcaccgac ttcaccctga caatcagcag actggaaccc    240

gaggacttcg ccgtgtacta ctgccagcag agaagcaact ggcccatcac attcggccag    300

ggcaccaagc tggaaatcaa gcgaactgtg gctgcaccat ctgtcttcat cttcccgcca    360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat    420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag    480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg    540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc    600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                       642
```

<210> SEQ ID NO 56
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 56

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Thr Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Ala Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
        355                 360                 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
```

-continued

385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

Lys

<210> SEQ ID NO 57
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

gaagtgcagc tgctggaatc tggtggcgga gttgttcagc ctggcggctc tctgagactg 60

tcttgtgctg ccagcggctt caccttcaac gactacgcta tgcactgggt ccgacaggcc 120

cctggcaaag gacttgaatg ggtgtccacc atcagctgga acagcggctc tatcggctac 180

gccgattccg tgaagggcag attcaccatc tccagagaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag agccgaggac accgccgtgt actactgtgc caaggacatc 300

cagtacggca actactacta cggcatggac tactggggcc agggaacact ggttaccgtt 360

agctctgcta gcaccaaggg ccccagcgtg ttccccctgg ccccttgcag cagaagcacc 420

agcgagagca cagccgccct gggctgcctg gtgaaggact acttccccga gcccgtgacc 480

gtgtcctgga acagcggcgc tctgaccagc ggcgtgcata ccttccccgc cgtgctccag 540

agcagcggac tgtactccct gagcagcgtg gtgaccgtgc cttccagcag cctgggcacc 600

aagacctaca cctgcaacgt ggaccacaag cccagcaaca ccaaggtgga caagagagtg 660

gagagcaagt acggccctcc ctgccccct tgccctgccc ccgagttcga gggcggacct 720

agcgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagcag aacccccgag 780

gtgacctgcg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt taattggtac 840

gtggacggcg tggaagtgca taacgccaag accaagccca gagaggagca gttcaacagc 900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa 960

tacaagtgca aggtctccaa caagggcctg gccagcagca tcgagaagac catcagcaag 1020

gccaagggcc agccacggga gccccaggtc tgcaccctgc cacctagcca agaggagatg 1080

accaagaacc aggtgtccct gagctgtgcc gtgaaaggct tctatcccag cgatatcgcc 1140

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg 1200

gacagcgacg gcagcttctt cctggtttcc aagctgaccg tggacaagtc cagatggcag 1260

gagggcaacg tcttcagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 1320

aagtccctga gcctgagcct gggcaag 1347

<210> SEQ ID NO 58
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly

-continued

```
1               5                   10                  15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205

Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 59
<211> LENGTH: 645
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

caggctgtgg tcacacaaga gcctagcctg acagtgtctc ctggcggcac agtgaccctg     60

acctgtagat cttctacagg cgccgtgacc accagcaact acgctaattg ggtgcagcag    120

aagcccggcc aggctcctag aggactgatc ggcggaacaa acaagagagc cccttggaca    180

cccgccagat tctctggatc tctgctcggc ggaaaggccg ctctgacaat cactggtgct    240

caggctgagg acgaggccga gtactattgt gtgctgtggt acagcaacct gtgggtgttc    300

ggcggaggca ccaaactgac agttctgggt cagcccaagg cggcgccctc ggtcactctg    360

ttcccgccct cctctgagga gcttcaagcc aacaaggcca cactggtgtg tctcataagt    420

gacttctatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg    480

ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctac    540

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat    600

gaagggagca ccgtggagaa gacagtggcc cctacagaat gttca                    645


<210> SEQ ID NO 60
<211> LENGTH: 452
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
```

-continued

<400> SEQUENCE: 60

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
            20                  25                  30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
    130                 135                 140

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys
        195                 200                 205

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
    210                 215                 220

Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Ala Ser Ser
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Cys Gln Glu Glu Met Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
```

-continued

```
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Leu Gly Lys
    450
```

<210> SEQ ID NO 61
<211> LENGTH: 1356
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

```
gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg     60

tcttgtgccg ccagcggctt caccttcaac acctacgcta tgaactgggt ccgacaggcc    120

cctggcaaag gactggaatg ggtgggaaga atcaggtcca agtacaacaa ctacgccacc    180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacagc    240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgtgtcaga    300

cacggcaact tcggcaacag ctatgtgtct tggtttgcct actggggcca gggcacactg    360

gtcacagtta gctctgctag caccaagggc cccagcgtgt tccccctggc cccttgcagc    420

agaagcacca gcgagagcac agccgccctg ggctgcctgg tgaaggacta cttccccgag    480

cccgtgaccg tgtcctggaa cagcggcgct ctgaccagcg gcgtgcatac cttccccgcc    540

gtgctccaga gcagcggact gtactccctg agcagcgtgg tgaccgtgcc ttccagcagc    600

ctgggcacca agacctacac ctgcaacgtg gaccacaagc ccagcaacac caaggtggac    660

aagagagtgg agagcaagta cggccctccc tgccccctt gccctgcccc cgagttcgag    720

ggcggaccta gcgtgttcct gttcccccc aagcccaagg acaccctgat gatcagcaga    780

acccccgagg tgacctgcgt ggtggtggac gtgtcccagg aggaccccga ggtccagttt    840

aattggtacg tggacggcgt ggaagtgcat aacgccaaga ccaagcccag agaggagcag    900

ttcaacagca cctacagagt ggtgtccgtg ctgaccgtgc tgcaccagga ctggctgaac    960

ggcaaggaat acaagtgcaa ggtctccaac aagggcctgg ccagcagcat cgagaagacc   1020

atcagcaagg ccaagggcca gccacgggag ccccaggtct acaccctgcc accttgtcaa   1080

gaggagatga ccaagaacca ggtgtccctg tggtgtctgg tgaaaggctt ctatcccagc   1140

gatatcgccg tggagtggga gagcaacggc cagcccgaga acaactacaa gaccaccccc   1200

cctgtgctgg acagcgacgg cagcttcttc ctgtactcca agctgaccgt ggacaagtcc   1260

agatggcagg agggcaacgt cttcagctgc tccgtgatgc acgaggccct gcacaaccac   1320

tacacccaga agtccctgag cctgagcctg ggcaag                             1356
```

<210> SEQ ID NO 62
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

-continued

```
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Lys Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Ile
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> SEQ ID NO 63
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

```
gagatcgtgc tgacacagag ccctggcaca ctgtcactgt ctccaggcga gagagccaca     60

ctgagctgta gagccagcca gagcgtgtcc tcttacctgg cctggtatca gaagaagcct    120

ggacaggctc ccagactgct gatctacgac gccagcaaca gagccacagg catccccgat    180

agattcagcg gctctggctc tggcaccgac ttcaccctga caatcagcag actggaaccc    240

gaggacttcg ccgtgtacta ctgccagcag agaagcaact ggcccatcac attcggccag    300

ggcaccaagc tggaaatcaa gcgaactgtg gctgcaccat ctgtcttcat cttcccgcca    360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat    420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag    480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg    540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc    600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                       642
```

<210> SEQ ID NO 64
<211> LENGTH: 449
<212> TYPE: PRT

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Glu Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Thr Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Ala Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
        355                 360                 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380
```

-continued

```
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445

Lys
```

<210> SEQ ID NO 65
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

```
gaagtgcagc tgctggaatc tggtggcgga gttgttcagc ctggcggctc tctgagactg     60

tcttgtgctg ccagcggctt caccttcaac gactacgcta tgcactgggt ccgagaggcc    120

cctggcaaag gacttgaatg ggtgtccacc atcagctgga acagcggctc tatcggctac    180

gccgattccg tgaagggcag attcaccatc tccagagaca acagcaagaa caccctgtac    240

ctgcagatga acagcctgag agccgaggac accgccgtgt actactgtgc caaggacatc    300

cagtacggca actactacta cggcatggac tactggggcc agggaacact ggttaccgtt    360

agctctgcta gcaccaaggg ccccagcgtg ttccccctgg ccccttgcag cagaagcacc    420

agcgagagca cagccgccct gggctgcctg gtgaaggact acttccccga gcccgtgacc    480

gtgtcctgga acagcggcgc tctgaccagc ggcgtgcata ccttccccgc cgtgctccag    540

agcagcggac tgtactccct gagcagcgtg gtgaccgtgc cttccagcag cctgggcacc    600

aagacctaca cctgcaacgt ggaccacaag cccagcaaca ccaaggtgga caagagagtg    660

gagagcaagt acggccctcc ctgccccct tgccctgccc ccgagttcga gggcggacct    720

agcgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagcag aacccccgag    780

gtgacctgcg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt taattggtac    840

gtggacggcg tggaagtgca taacgccaag accaagccca gagaggagca gttcaacagc    900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa    960

tacaagtgca aggtctccaa caagggcctg gccagcagca tcgagaagac catcagcaag   1020

gccaagggcc agccacggga gccccaggtc tgcaccctgc cacctagcca agaggagatg   1080

accaagaacc aggtgtccct gagctgtgcc gtgaaaggct tctatcccag cgatatcgcc   1140

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg   1200

gacagcgacg gcagcttctt cctggtttcc aagctgaccg tggacaagtc cagatggcag   1260

gagggcaacg tcttcagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag   1320

aagtccctga gcctgagcct gggcaag                                       1347
```

<210> SEQ ID NO 66
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

-continued

```
Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205

Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 67
<211> LENGTH: 645
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

caggctgtgg tcacacaaga gcctagcctg acagtgtctc ctggcggcac agtgaccctg     60

acctgtagat cttctacagg cgccgtgacc accagcaact acgctaattg ggtgcaggag    120

aagcccggcc aggctcctag aggactgatc ggcggaacaa acaagagagc cccttggaca    180

cccgccagat tctctggatc tctgctcggc ggaaaggccg ctctgacaat cactggtgct    240

caggctgagg acgaggccga gtactattgt gtgctgtggt acagcaacct gtgggtgttc    300

ggcggaggca ccaaactgac agttctgggt cagcccaagg cggcgccctc ggtcactctg    360

ttcccgccct cctctgagga gcttcaagcc aacaaggcca cactggtgtg tctcataagt    420

gacttctatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg    480

ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctac    540

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat    600

gaagggagca ccgtggagaa gacagtggcc cctacagaat gttca                    645


<210> SEQ ID NO 68
<211> LENGTH: 452
<212> TYPE: PRT
```

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
            20                  25                  30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
    130                 135                 140

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys
        195                 200                 205

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
    210                 215                 220

Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Ala Ser Ser
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Cys Gln Glu Glu Met Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380
```

-continued

```
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Leu Gly Lys
    450
```

<210> SEQ ID NO 69
<211> LENGTH: 1356
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

```
gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg     60

tcttgtgccg ccagcggctt caccttcaac acctacgcta tgaactgggt ccgaaaggcc    120

cctggcaaag gactggaatg ggtgggaaga atcaggtcca agtacaacaa ctacgccacc    180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacagc    240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgtgtcaga    300

cacggcaact tcggcaacag ctatgtgtct tggtttgcct actggggcca gggcacactg    360

gtcacagtta gctctgctag caccaagggc cccagcgtgt tccccctggc cccttgcagc    420

agaagcacca gcgagagcac agccgccctg ggctgcctgg tgaaggacta cttccccgag    480

cccgtgaccg tgtcctggaa cagcggcgct ctgaccagcg gcgtgcatac cttccccgcc    540

gtgctccaga gcagcggact gtactccctg agcagcgtgg tgaccgtgcc ttccagcagc    600

ctgggcacca agacctacac ctgcaacgtg gaccacaagc ccagcaacac caaggtggac    660

aagagagtgg agagcaagta cggccctccc tgccccctt gccctgcccc cgagttcgag    720

ggcggaccta gcgtgttcct gttcccccc aagcccaagg acaccctgat gatcagcaga    780

acccccgagg tgacctgcgt ggtggtggac gtgtcccagg aggaccccga ggtccagttt    840

aattggtacg tggacggcgt ggaagtgcat aacgccaaga ccaagcccag agaggagcag    900

ttcaacagca cctacagagt ggtgtccgtg ctgaccgtgc tgcaccagga ctggctgaac    960

ggcaaggaat acaagtgcaa ggtctccaac aagggcctgg ccagcagcat cgagaagacc   1020

atcagcaagg ccaagggcca gccacgggag ccccaggtct acaccctgcc accttgtcaa   1080

gaggagatga ccaagaacca ggtgtccctg tggtgtctgg tgaaaggctt ctatcccagc   1140

gatatcgccg tggagtggga gagcaacggc cagcccgaga acaactacaa gaccaccccc   1200

cctgtgctgg acagcgacgg cagcttcttc ctgtactcca agctgaccgt ggacaagtcc   1260

agatggcagg agggcaacgt cttcagctgc tccgtgatgc acgaggccct gcacaaccac   1320

tacacccaga agtccctgag cctgagcctg ggcaag                              1356
```

<210> SEQ ID NO 70
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

-continued

```
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Lys Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Ile
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Lys Lys Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

<210> SEQ ID NO 71
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

```
gagatcgtgc tgacacagag ccctggcaca ctgtcactgt ctccaggcga gagagccaca     60

ctgagctgta gagccagcca gagcgtgtcc tcttacctgg cctggtatca gaagaagcct    120

ggacaggctc ccagactgct gatctacgac gccagcaaca gagccacagg catccccgat    180

agattcagcg gctctggctc tggcaccgac ttcaccctga caatcagcag actggaaccc    240

gaggacttcg ccgtgtacta ctgccagcag agaagcaact ggcccatcac attcggccag    300

ggcaccaagc tggaaatcaa gcgaactgtg gctgcaccat ctgtcttcat cttcccgcca    360

tctgataaga aattgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat    420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag    480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg    540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc    600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                       642
```

<210> SEQ ID NO 72
<211> LENGTH: 449

-continued

<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asp Tyr
20 25 30

Ala Met His Trp Val Arg Glu Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Glu Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Glu Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Ala Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
355 360 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

-continued

```
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445

Lys
```

<210> SEQ ID NO 73
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

```
gaagtgcagc tgctggaatc tggtggcgga gttgttcagc ctggcggctc tctgagactg     60

tcttgtgctg ccagcggctt caccttcaac gactacgcta tgcactgggt ccgagaggcc    120

cctggcaaag gacttgaatg ggtgtccacc atcagctgga acagcggctc tatcggctac    180

gccgattccg tgaagggcag attcaccatc tccagagaca acagcaagaa caccctgtac    240

ctgcagatga acagcctgag agccgaggac accgccgtgt actactgtgc caaggacatc    300

cagtacggca actactacta cggcatggac tactggggcc agggaacact ggttaccgtt    360

agctctgcta gcaccaaggg ccccagcgtg ttccccctgg ccccttgcag cagaagcacc    420

agcgagagca cagccgccct gggctgcctg gtggaggact acttccccga gcccgtgacc    480

gtgtcctgga acagcggcgc tctgaccagc ggcgtgcata ccttccccgc cgtgctccag    540

agcagcggac tgtactccct gagcagcgtg gtgaccgtgc cttccagcag cctgggcacc    600

aagacctaca cctgcaacgt ggaccacaag cccagcaaca ccaaggtgga cgagagagtg    660

gagagcaagt acggccctcc ctgcccccct tgccctgccc ccgagttcga aggcggacct    720

agcgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagcag aaccccgag     780

gtgacctgcg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt taattggtac    840

gtggacggcg tggaagtgca taacgccaag accaagccca gagaggagca gttcaacagc    900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa    960

tacaagtgca aggtctccaa caagggcctg gccagcagca tcgagaagac catcagcaag   1020

gccaagggcc agccacggga gccccaggtc tgcaccctgc cacctagcca agaggagatg   1080

accaagaacc aggtgtccct gagctgtgcc gtgaaaggct tctatcccag cgatatcgcc   1140

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg   1200

gacagcgacg gcagcttctt cctggtttcc aagctgaccg tggacaagtc cagatggcag   1260

gagggcaacg tcttcagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag   1320

aagtccctga gcctgagcct gggcaag                                       1347
```

<210> SEQ ID NO 74
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

-continued

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Glu Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Thr Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Glu Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Glu Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
        355                 360                 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400
```

-continued

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

Lys

<210> SEQ ID NO 75
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

gaagtgcagc tgctggaatc tggtggcgga gttgttcagc ctggcggctc tctgagactg 60

tcttgtgctg ccagcggctt caccttcaac gactacgcta tgcactgggt ccgagaggcc 120

cctggcaaag gacttgaatg ggtgtccacc atcagctgga acagcggctc tatcggctac 180

gccgattccg tgaagggcag attcaccatc tccagagaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgag agccgaggac accgccgtgt actactgtgc caaggacatc 300

cagtacggca actactacta cggcatggac tactggggcc agggaacact ggttaccgtt 360

agctctgcta gcaccaaggg ccccagcgtg ttccccctgg ccccttgcag cagaagcacc 420

agcgagagca cagccgccct gggctgcctg gtggaggact acttccccga gcccgtgacc 480

gtgtcctgga acagcggcgc tctgaccagc ggcgtgcata ccttccccgc cgtgctccag 540

agcagcggac tgtactccct gagcagcgtg gtgaccgtgc cttccagcag cctgggcacc 600

aagacctaca cctgcaacgt ggaccacaag cccagcaaca ccaaggtgga cgagagagtg 660

gagagcaagt acggccctcc ctgcccccct tgccctgccc ccgagttcga aggcggacct 720

agcgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagcag aacccccgag 780

gtgacctgcg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt taattggtac 840

gtggacggcg tggaagtgca taacgccaag accaagccca gagaggagca gttcgccagc 900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa 960

tacaagtgca aggtctccaa caagggcctg cctagcagca tcgagaagac catcagcaag 1020

gccaagggcc agccacggga gccccaggtc tgcaccctgc cacctagcca agaggagatg 1080

accaagaacc aggtgtccct gagctgtgcc gtgaaaggct tctatcccag cgatatcgcc 1140

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg 1200

gacagcgacg gcagcttctt cctggtttcc aagctgaccg tggacaagtc cagatggcag 1260

gagggcaacg tcttcagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 1320

aagtccctga gcctgagcct gggcaag 1347

<210> SEQ ID NO 76
<211> LENGTH: 223
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

-continued

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
            20                  25                  30

Ala Met Asn Trp Val Arg Lys Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
        115                 120                 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
    130                 135                 140

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
145                 150                 155                 160

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
                165                 170                 175

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
            180                 185                 190

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys
        195                 200                 205

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
    210                 215                 220
```

<210> SEQ ID NO 77
<211> LENGTH: 669
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

```
gaggtgcagc tggttgaatc tggcggagga ctggttcagc ctggcggatc tctgagactg     60

tcttgtgccg ccagcggctt caccttcaac acctacgcta tgaactgggt ccgaaaggcc    120

cctggcaaag gactggaatg ggtgggaaga atcaggtcca agtacaacaa ctacgccacc    180

tactacgccg acagcgtgaa ggacagattc accatcagca gggacgacag caagaacagc    240

ctgtacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgtgtcaga    300

cacggcaact tcggcaacag ctatgtgtct tggtttgcct actggggcca gggcacactg    360

gtcacagtta gctctgctag caccaagggc cccagcgtgt tccccctggc cccttgcagc    420

agaagcacca gcgagagcac agccgccctg ggctgcctgg tgaaggacta cttccccgag    480

cccgtgaccg tgtcctggaa cagcggcgct ctgaccagcg gcgtgcatac cttccccgcc    540

gtgctccaga gcagcggact gtactccctg agcagcgtgg tgaccgtgcc ttccagcagc    600

ctgggcacca agacctacac ctgcaacgtg gaccacaagc ccagcaacac caaggtggac    660

aagagagtg                                                            669
```

<210> SEQ ID NO 78
<211> LENGTH: 444
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 78

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205

Val Ala Pro Thr Glu Cys Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro
210 215 220

Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe
225 230 235 240

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
245 250 255

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
260 265 270

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
275 280 285

Arg Glu Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr
290 295 300

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305 310 315 320

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
325 330 335

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Gln
340 345 350

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
355 360 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
370 375 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

-continued

385 390 395 400

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
405 410 415

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
420 425 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440

<210> SEQ ID NO 79
<211> LENGTH: 1332
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

caggctgtgg tcacacaaga gcctagcctg acagtgtctc ctggcggcac agtgaccctg 60

acctgtagat cttctacagg cgccgtgacc accagcaact acgctaattg ggtgcaggag 120

aagcccggcc aggctcctag aggactgatc ggcggaacaa acaagagagc cccttggaca 180

cccgccagat tctctggatc tctgctcggc ggaaaggccg ctctgacaat cactggtgct 240

caggctgagg acgaggccga gtactattgt gtgctgtggt acagcaacct gtgggtgttc 300

ggcggaggca ccaaactgac agttctgggt cagcccaagg cggcgccctc ggtcactctg 360

ttcccgccct cctctgagga gcttcaagcc aacaaggcca cactggtgtg tctcataagt 420

gacttctatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480

ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctac 540

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600

gaagggagca ccgtggagaa gacagtggcc cctacagaat gttcagagag caagtacggc 660

cctccctgcc ccccttgccc tgcccccgag ttcgagggcg gacctagcgt gttcctgttc 720

ccccccaagc ccaaggacac cctgatgatc agcagaaccc ccgaggtgac ctgcgtggtg 780

gtggacgtgt cccaggagga ccccgaggtc cagtttaatt ggtacgtgga cggcgtggaa 840

gtgcataacg ccaagaccaa gcccagagag gagcagttcg ccagcaccta cagagtggtg 900

tccgtgctga ccgtgctgca ccaggactgg ctgaacggca aggaatacaa gtgcaaggtc 960

tccaacaagg gcctgcctag cagcatcgag aagaccatca gcaaggccaa gggccagcca 1020

cgggagcccc aggtctacac cctgccacct tgtcaagagg agatgaccaa gaaccaggtg 1080

tccctgtggt gtctggtgaa aggcttctat cccagcgata tcgccgtgga gtgggagagc 1140

aacggccagc ccgagaacaa ctacaagacc acccccctg tgctggacag cgacggcagc 1200

ttcttcctgt actccaagct gaccgtggac aagtccagat ggcaggaggg caacgtcttc 1260

agctgctccg tgatgcacga ggccctgcac aaccactaca cccagaagtc cctgagcctg 1320

agcctgggca ag 1332

<210> SEQ ID NO 80
<211> LENGTH: 218
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1 5 10 15

-continued

```
Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Lys Ser Val Ser Thr Ser
            20                  25                  30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Lys Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65                  70                  75                  80

Pro Val Glu Ala Glu Asp Thr Ala Asn Tyr Tyr Cys Gln His Ser Arg
                85                  90                  95

Glu Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105                 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
        195                 200                 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> SEQ ID NO 81
<211> LENGTH: 654
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

```
gacatcgtgc tgacacagag ccctgcttct ctggctgtgt ctcctggcca gagagccacc     60

atcacctgta gagccagcaa gagcgtgtcc accagcggct actcttacat gcactggtat    120

cagaagaagc ccggccagcc tcctaagctg ctgatctacc tggctagcaa cctcgaaagc    180

ggagtgcctg ctagattttc tggcagcggc tctggcaccg acttcaccct gacaatcaac    240

cccgtggaag ccgaagacac cgccaactac tactgccagc acagcagaga gctgccctgg    300

acatttggcc agggcaccaa ggtggaaatc aagcgaactg tggctgcacc atctgtcttc    360

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg    420

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg    480

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc    540

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc    600

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt          654
```

<210> SEQ ID NO 82
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

-continued

```
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asn Phe
            20                  25                  30

Gly Met Asn Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Gln Ile Tyr Ala Asp Gly Phe
    50                  55                  60

Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Val Gly Phe Val Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Ala Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
        355                 360                 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400
```

-continued

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

Lys

<210> SEQ ID NO 83
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

caggttcagc tggtgcagtc tggcagcgag ctgaagaaac ctggcgcctc tgtgaaggtg 60

tcctgcaagg ctagcggcta catcttcacc aacttcggca tgaactgggt ccgagaggct 120

cctggacagg gactcgaatg gatgggctgg atcaacacct acaccggcga gcagatctac 180

gccgatggct tcacaggcag attcgtgttc agcctggaca ccagcgccag cacagcttac 240

ctgcagatca gctctctgaa ggccgaggat accgccgtgt acttctgtgc cagaggcgag 300

atctactacg gctacgacgt gggctttgtg tactggggcc agggaacact ggtcaccgtt 360

agctctgcta gcaccaaggg ccccagcgtg ttccccctgg ccccttgcag cagaagcacc 420

agcgagagca cagccgccct gggctgcctg gtgaaggact acttccccga gcccgtgacc 480

gtgtcctgga acagcggcgc tctgaccagc ggcgtgcata ccttccccgc cgtgctccag 540

agcagcggac tgtactccct gagcagcgtg gtgaccgtgc cttccagcag cctgggcacc 600

aagacctaca cctgcaacgt ggaccacaag cccagcaaca ccaaggtgga caagagagtg 660

gagagcaagt acggccctcc ctgcccccct tgccctgccc ccgagttcga gggcggacct 720

agcgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagcag aacccccgag 780

gtgacctgcg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt taattggtac 840

gtggacggcg tggaagtgca taacgccaag accaagccca gagaggagca gttcaacagc 900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa 960

tacaagtgca aggtctccaa caagggcctg gccagcagca tcgagaagac catcagcaag 1020

gccaagggcc agccacggga gccccaggtc tgcaccctgc cacctagcca agaggagatg 1080

accaagaacc aggtgtccct gagctgtgcc gtgaaaggct tctatcccag cgatatcgcc 1140

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg 1200

gacagcgacg gcagcttctt cctggtttcc aagctgaccg tggacaagtc cagatggcag 1260

gagggcaacg tcttcagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 1320

aagtccctga gcctgagcct gggcaag 1347

<210> SEQ ID NO 84
<211> LENGTH: 218
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
1 5 10 15

-continued

```
Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Lys Ser Val Thr Thr Ser
            20                  25                  30

Gly Tyr Ser Tyr Ile His Trp Tyr Gln Lys Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Leu Leu Ile Tyr Leu Ala Ser Asp Leu Glu Ala Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
65                  70                  75                  80

Pro Val Glu Ala Glu Asp Thr Ala Asn Tyr Tyr Cys Gln His Ser Arg
                85                  90                  95

Glu Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105                 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
        195                 200                 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> SEQ ID NO 85
<211> LENGTH: 654
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

```
gacatcgtgc tgacacagag ccctgcttct ctggctgtgt ctcctggcca gagagccacc     60

atcacctgta gagccagcaa gagcgtgacc accagcggct actcttacat ccactggtat    120

cagaagaagc ccggccagcc tcctaagctg ctgatctacc tggccagcga tctggaagct    180

ggcgtgccag ctagattttc tggcagcggc tctggcaccg acttcaccct gacaatcaac    240

cccgtggaag ccgaagacac cgccaactac tactgccagc acagcagaga gctgccctgg    300

acatttggcc agggcaccaa ggtggaaatc aagcgaactg tggctgcacc atctgtcttc    360

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg    420

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg    480

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc    540

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc    600

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt          654
```

<210> SEQ ID NO 86
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

-continued

```
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asn Phe
            20                  25                  30

Gly Met Asn Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Gln Ile Tyr Ala Asp Gly Phe
    50                  55                  60

Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Val Gly Phe Val Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
    210                 215                 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
            260                 265                 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Ala Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
            340                 345                 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
        355                 360                 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400
```

-continued

```
Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440                 445

Lys
```

<210> SEQ ID NO 87
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

```
caggttcagc tggtgcagtc tggcagcgag ctgaagaaac ctggcgcctc tgtgaaggtg     60

tcctgcaagg ctagcggcta catcttcacc aacttcggca tgaactgggt ccgagaggct    120

cctggacagg gactcgaatg gatgggctgg atcaacacct acaccggcga gcagatctac    180

gccgatggct tcacaggcag attcgtgttc agcctggaca ccagcgccag cacagcttac    240

ctgcagatca gctctctgaa ggccgaggat accgccgtgt acttctgtgc cagaggcgag    300

atctactacg gctacgacgt gggctttgtg tactggggcc agggaacact ggtcaccgtt    360

agctctgcta gcaccaaggg ccccagcgtg ttccccctgg ccccttgcag cagaagcacc    420

agcgagagca cagccgccct gggctgcctg gtgaaggact acttccccga gcccgtgacc    480

gtgtcctgga acagcggcgc tctgaccagc ggcgtgcata ccttccccgc cgtgctccag    540

agcagcggac tgtactccct gagcagcgtg gtgaccgtgc cttccagcag cctgggcacc    600

aagacctaca cctgcaacgt ggaccacaag cccagcaaca ccaaggtgga caagagagtg    660

gagagcaagt acggccctcc ctgcccccct tgccctgccc ccgagttcga gggcggacct    720

agcgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagcag aacccccgag    780

gtgacctgcg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt taattggtac    840

gtggacggcg tggaagtgca taacgccaag accaagccca gagaggagca gttcaacagc    900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa    960

tacaagtgca aggtctccaa caagggcctg gccagcagca tcgagaagac catcagcaag   1020

gccaagggcc agccacggga gccccaggtc tgcaccctgc cacctagcca agaggagatg   1080

accaagaacc aggtgtccct gagctgtgcc gtgaaaggct tctatcccag cgatatcgcc   1140

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg   1200

gacagcgacg gcagcttctt cctggtttcc aagctgaccg tggacaagtc cagatggcag   1260

gagggcaacg tcttcagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag   1320

aagtccctga gcctgagcct gggcaag                                       1347
```

<210> SEQ ID NO 88
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15
```

-continued

```
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
            20                  25                  30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Lys Lys Pro Gly Gln Ser
        35                  40                  45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Leu Gln Val
                85                  90                  95

Thr His Val Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 89
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

gacgtggtca tgacacagag ccctctgagc ctgcctgtga cacctggcga acctgccagc     60

atcagctgta gaagcagcca gagcatcgtg cacagcaacg gcaacacata cctggagtgg    120

tatctgaaga agcccggcca gtctcctcag ctgctgatct acaaggtgtc caacagattc    180

agcggcgtgc ccgacagatt ctctggctct ggatctggca ccgacttcac cctgaagatc    240

tccagagtgg aagccgagga cgtgggcgtg tacttctgtc tccaggtcac acacgtgccc    300

ctgacatttg gccagggcac caagctggaa atcaagcgaa ctgtggctgc accatctgtc    360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg    420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa    480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc    540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa    600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt       657


<210> SEQ ID NO 90
<211> LENGTH: 442
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90
```

-continued

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ala Asp Tyr
            20                  25                  30

Glu Ile His Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ala Ile His Pro Gly Ser Gly Gly Thr Ala Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Leu Thr Ala Asp Glu Ser Ser Thr Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Tyr Tyr Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
        115                 120                 125

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
    130                 135                 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145                 150                 155                 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
                165                 170                 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
            180                 185                 190

Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
        195                 200                 205

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Gly Leu Ala Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Gln Glu Glu
            340                 345                 350

Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400
```

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```
Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
                405                 410                 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440
```

<210> SEQ ID NO 91
<211> LENGTH: 1326
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

```
caggttcagc tggttcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg     60

tcctgcaagg ctagcggcta caccttcgcc gactacgaga tccactgggt ccgagaggct    120

ccaggacagg gacttgaatg gatgggcgct atccatcctg gctctggcgg cacagcttac    180

gcccagaaat tccagggcag agtgaccctg accgccgacg agtctagcac caccgcctac    240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcac ccggtactac    300

agcttcgcct actggggaca gggaaccctg gtcacagtca gctctgctag caccaagggc    360

cccagcgtgt tccccctggc cccttgcagc agaagcacca gcgagagcac agccgccctg    420

ggctgcctgg tgaaggacta cttccccgag cccgtgaccg tgtcctggaa cagcggcgct    480

ctgaccagcg gcgtgcatac cttccccgcc gtgctccaga gcagcggact gtactccctg    540

agcagcgtgg tgaccgtgcc ttccagcagc ctgggcacca agacctacac ctgcaacgtg    600

gaccacaagc ccagcaacac caaggtggac aagagagtgg agagcaagta cggccctccc    660

tgccccctt gccctgcccc cgagttcgag ggcggaccta gcgtgttcct gttcccccc     720

aagcccaagg acaccctgat gatcagcaga acccccgagg tgacctgcgt ggtggtggac    780

gtgtcccagg aggaccccga ggtccagttt aattggtacg tggacggcgt ggaagtgcat    840

aacgccaaga ccaagcccag agaggagcag ttcaacagca cctacagagt ggtgtccgtg    900

ctgaccgtgc tgcaccagga ctggctgaac ggcaaggaat acaagtgcaa ggtctccaac    960

aagggcctgg ccagcagcat cgagaagacc atcagcaagg ccaagggcca gccacgggag   1020

ccccaggtct gcaccctgcc acctagccaa gaggagatga ccaagaacca ggtgtccctg   1080

agctgtgccg tgaaaggctt ctatcccagc gatatcgccg tggagtggga gagcaacggc   1140

cagcccgaga acaactacaa gaccaccccc cctgtgctgg acagcgacgg cagcttcttc   1200

ctggtttcca agctgaccgt ggacaagtcc agatggcagg agggcaacgt cttcagctgc   1260

tccgtgatgc acgaggccct gcacaaccac tacacccaga agtccctgag cctgagcctg   1320

ggcaag                                                              1326
```

<210> SEQ ID NO 92
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
            20                  25                  30
```

-continued

```
Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Lys Lys Pro Gly Gln Ser
        35                  40                  45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Leu Gln Val
                85                  90                  95

Thr His Val Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Lys
        115                 120                 125

Lys Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> SEQ ID NO 93
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

```
gacgtggtca tgacacagag ccctctgagc ctgcctgtga cacctggcga acctgccagc     60

atcagctgta gaagcagcca gagcatcgtg cacagcaacg gcaacacata cctggagtgg    120

tatctgaaga agcccggcca gtctcctcag ctgctgatct acaaggtgtc caacagattc    180

agcggcgtgc ccgacagatt ctctggctct ggatctggca ccgacttcac cctgaagatc    240

tccagagtgg aagccgagga cgtgggcgtg tacttctgtc tccaggtcac acacgtgccc    300

ctgacatttg gccagggcac caagctggaa atcaagcgaa ctgtggctgc accatctgtc    360

ttcatcttcc cgccatctga taagaaattg aaatctggaa ctgcctctgt tgtgtgcctg    420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa    480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc    540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa    600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt       657
```

<210> SEQ ID NO 94
<211> LENGTH: 442
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
```

-continued

```
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ala Asp Tyr
            20                  25                  30

Glu Ile His Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ala Ile His Pro Gly Ser Gly Gly Thr Ala Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Leu Thr Ala Asp Glu Ser Ser Thr Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Tyr Tyr Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
        115                 120                 125

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
    130                 135                 140

Glu Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145                 150                 155                 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
                165                 170                 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
            180                 185                 190

Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
        195                 200                 205

Val Asp Glu Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
    210                 215                 220

Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
225                 230                 235                 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                245                 250                 255

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
            260                 265                 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        275                 280                 285

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    290                 295                 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305                 310                 315                 320

Lys Gly Leu Ala Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                325                 330                 335

Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Gln Glu Glu
            340                 345                 350

Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
        355                 360                 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    370                 375                 380

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
385                 390                 395                 400

Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
                405                 410                 415
```

-continued

```
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            420                 425                 430

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440


<210> SEQ ID NO 95
<211> LENGTH: 1326
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

caggttcagc tggttcagtc tggcgccgaa gtgaagaaac ctggcagcag cgtgaaggtg     60

tcctgcaagg ctagcggcta caccttcgcc gactacgaga tccactgggt ccgagaggct    120

ccaggacagg gacttgaatg gatgggcgct atccatcctg gctctggcgg cacagcttac    180

gcccagaaat tccagggcag agtgaccctg accgccgacg agtctagcac caccgcctac    240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcac ccggtactac    300

agcttcgcct actggggaca gggaaccctg gtcacagtca gctctgctag caccaagggc    360

cccagcgtgt tccccctggc cccttgcagc agaagcacca gcgagagcac agccgccctg    420

ggctgcctgg tggaggacta cttccccgag cccgtgaccg tgtcctggaa cagcggcgct    480

ctgaccagcg gcgtgcatac cttccccgcc gtgctccaga gcagcggact gtactccctg    540

agcagcgtgg tgaccgtgcc ttccagcagc ctgggcacca agacctacac ctgcaacgtg    600

gaccacaagc ccagcaacac caaggtggac gagagagtgg agagcaagta cggccctccc    660

tgcccccctt gccctgcccc cgagttcgaa ggcggaccta gcgtgttcct gttcccccca    720

aagcccaagg acaccctgat gatcagcaga acccccgagg tgacctgcgt ggtggtggac    780

gtgtcccagg aggaccccga ggtccagttt aattggtacg tggacggcgt ggaagtgcat    840

aacgccaaga ccaagcccag agaggagcag ttcaacagca cctacagagt ggtgtccgtg    900

ctgaccgtgc tgcaccagga ctggctgaac ggcaaggaat acaagtgcaa ggtctccaac    960

aagggcctgg ccagcagcat cgagaagacc atcagcaagg ccaagggcca gccacgggag   1020

ccccaggtct gcaccctgcc acctagccaa gaggagatga ccaagaacca ggtgtccctg   1080

agctgtgccg tgaaaggctt ctatcccagc gatatcgccg tggagtggga gagcaacggc   1140

cagcccgaga acaactacaa gaccaccccc cctgtgctgg acagcgacgg cagcttcttc   1200

ctggtttcca agctgaccgt ggacaagtcc agatggcagg agggcaacgt cttcagctgc   1260

tccgtgatgc acgaggccct gcacaaccac tacacccaga agtccctgag cctgagcctg   1320

ggcaag                                                              1326
```

1. A bispecific antibody or antigen-binding fragment thereof comprising:

(a) a first antigen-binding portion or antigen-binding fragment thereof, the first antigen-binding portion comprises a first light chain and a first heavy chain, the first light chain is a κ light chain, the first antigen-binding portion comprises a first binding domain that binds to a first antigen; and

(b) a second antigen-binding portion or antigen-binding fragment thereof, the second antigen-binding portion comprises a second light chain and a second heavy chain, the second light chain is a λ light chain, the second antigen-binding portion comprises a second binding domain that binds to a second antigen.

2. The bispecific antibody or antigen-binding fragment thereof according to claim **1**, wherein the second antigen is a CD3 antigen;

preferably, a second light chain variable region of the second antigen-binding portion has a $Gln_{40}Glu$ mutation ($V\lambda_{CD3}$: $Gln_{40}Glu$); and a second heavy chain variable region of the second antigen-binding portion has a $Gln_{39}Lys$ mutation (VH_{CD3}: $Gln_{39}Lys$);

preferably, the second binding domain comprises a second light chain CDR selected from amino acid

sequences of SEQ ID NOs: 7-9, 14, 15, 20, 21 or any variant thereof, and/or a second heavy chain CDR selected from amino acid sequences of SEQ ID NOs: 26-28, 31, 34, 40, 43, 46, 47 or any variant thereof; and

preferably, the second binding domain comprises a second light chain CDR1 selected from any of amino acid sequences of SEQ ID NOs: 7, 14 or any variant thereof, a second light chain CDR2 selected from any of amino acid sequences of SEQ ID NOs: 8, 15, 20 or any variant thereof, a second light chain CDR3 selected from any of amino acid sequences of SEQ ID NOs: 9, 21 or any variant thereof, and/or a second heavy chain CDR1 selected from any of amino acid sequences of SEQ ID NOs: 26, 31, 46 or any variant thereof, a second heavy chain CDR2 selected from any of amino acid sequences of SEQ ID NOs: 27, 47 or any variant thereof, a second heavy chain CDR3 selected from any of amino acid sequences of SEQ ID NOs: 28, 34, 37, 40, 43 of or any variant thereof;

preferably, the second light chain CDR of the second binding domain is selected from: the second light chain CDR1, CDR2 and CDR3 sequences respectively comprising amino acid sequences of SEQ ID NOs: 7, 8, 9; the second light chain CDR1, CDR2 and CDR3 respectively comprising amino acid sequences of SEQ ID NOs: 14, 15, 9; the second light chain CDR1, CDR2 and CDR3 respectively comprising amino acid sequences of SEQ ID NOs: 7, 8, 21; the second light chain CDR1, CDR2 and CDR3 respectively comprising amino acid sequences of SEQ ID NOs: 7, 20, 21; and/or the heavy chain CDR of the second binding domain is selected from the second heavy chains CDR1, CDR2 and CDR3 respectively comprising amino acid sequences of SEQ ID NOs: 26, 27, 28; the second heavy chains CDR1, CDR2 and CDR3 respectively comprising amino acid sequences of SEQ ID NOs: 31, 27, 28; the second heavy chains CDR1, CDR2 and CDR3 respectively comprising amino acid sequences of SEQ ID NOs: 31, 27, 34; the second heavy chains CDR1, CDR2 and CDR3 respectively comprising amino acid sequences of SEQ ID NOs: 31, 27, 37; the second heavy chains CDR1, CDR2 and CDR3 respectively comprising amino acid sequences of SEQ ID NOs: 31, 27, 40; the second heavy chains CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 31, 27, 43; the second heavy chains CDR1, CDR2 and CDR3 respectively comprising the amino acid sequences of SEQ ID NOs: 46, 47, 28;

preferably, the second binding domain comprises a second light chain variable region selected from any of amino acid sequences of SEQ ID NOs: 5, 10, 12, 16, 18, 22 or any variant thereof, and/or a second heavy chain variable region selected from any of amino acid sequences of SEQ ID NOs: 24, 29, 32, 35, 38, 41, 44, 48, 50, 52 or any variant thereof,

preferably, the second binding domain comprises a second light chain variable region of an amino acid sequence of SEQ ID NO: 18 or any variant thereof, and a second heavy chain variable region of an amino acid sequence of SEQ ID NO: 24 or any variant thereof, preferably, the second binding domain comprises a second light chain variable region of an amino acid sequence of SEQ ID NO: 5 or any variant thereof, and a second heavy chain variable region of an amino acid sequence of SEQ ID NO: 48 or any variant thereof,

preferably, the second binding domain comprises a second light chain variable region of an amino acid sequence of SEQ ID NO: 18 or any variant thereof, and a second heavy chain variable region of an amino acid sequence of SEQ ID NO: 48 or any variant thereof, preferably, the second binding domain comprises a second light chain variable region of an amino acid sequence of SEQ ID NO: 5 or any variant thereof, and a second heavy chain variable region of an amino acid sequence of SEQ ID NO: 50 or any variant thereof,

preferably, the second binding domain comprises a second light chain variable region of an amino acid sequence of SEQ ID NO: 10 or any variant thereof, and a second heavy chain variable region of an amino acid sequence of SEQ ID NO: 50 or any variant thereof, preferably, the second binding domain comprises a second light chain variable region of an amino acid sequence of SEQ ID NO: 12 or any variant thereof, and a second heavy chain variable region of an amino acid sequence of SEQ ID NO: 50 or any variant thereof, preferably, the second binding domain comprises a second light chain variable region of an amino acid sequence of SEQ ID NO: 18 or any variant thereof, and a second heavy chain variable region of an amino acid sequence of SEQ ID NO: 50 or any variant thereof, preferably, the second light chain of the second antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 58 and 66; and/or the second heavy chain of the second antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 60 and 68; more preferably, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 58; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 60; more preferably, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66; and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

3. The bispecific antibody or antigen-binding fragment thereof according to claim **1**, wherein the first antigen is a tumor antigen;

preferably, the tumor antigen is selected from: CD19, CD20, CD22, CD30, CD38, CD72, CD180, CD171 (L1CAM), CD123, CD133, CD138, CD37, CD70, CD79a, CD79b, CD56, CD74, CD166, CD71, CLL-1/CLECK12A, ROR1, BCMA, GPC3, mesothelin, CD33/IL3Ra, c-Met, PSCA, PSMA, glycolipid F77, EGFRvIII, GD-2, MY-ESO-1, Her2, Her3, MUC1, MUC17, Claudin18 or MAGEA3,

more preferably, the tumor associated antigen is selected from CD20, BCMA and GPC3.

4. The bispecific antibody or antigen-binding fragment thereof according to claim **1**, wherein the first antigen is a CD20 antigen;

preferably, the first light chain variable region of the first antigen-binding portion has a $Gln_{38}Lys$ mutation ($V\kappa_{CD20}$: $Gln_{38}Lys$); more preferably, the first heavy chain variable region of the first antigen-binding portion has a $Gln_{39}Glu$ mutation (VH_{CD20}: $Gln_{39}Glu$);

preferably, the first light chain variable region of the first antigen-binding portion has a $Gln_{38}Lys$ mutation ($V\kappa_{CD20}$: $Gln_{38}Lys$), and the first light chain constant region has $Glu_{23}Lys$ and $Gln_{124}Lys$ mutations ($V\kappa$-Ck_{CD20}: $Gln_{38}Lys\backslash Glu_{123}Lys\backslash Gln_{124}Lys$); more preferably, the first heavy chain variable region of the first antigen-binding portion has a $Gln_{39}Glu$ mutation (VH_{CD20}: $Gln_{39}Glu$), and the first heavy chain constant region has $Lys_{152}Glu$ and $Lys_{218}Glu$ mutations (V_H-C_H1_{CD20}: $Gln_{39}Glu\backslash Lys_{152}Glu\backslash Lys_{218}Glu$).

5. The bispecific antibody or antigen-binding fragment thereof according to claim **4**, wherein the first light chain of the first antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 54, 62, and 70; and/or the first heavy chain of the first antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 56, 64, and 72;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 54, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 56;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 62, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 64;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 70, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 72;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 54, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 56, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 58, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 60;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 62, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 64, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 58, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 60;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 70, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 72, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 62, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 64, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 58, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 60;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 54, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 56, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

6. The bispecific antibody or antigen-binding fragment thereof according to claim **1**, wherein the first antigen is a BCMA antigen;

preferably, the first light chain variable region of the first antigen-binding portion has a $Gln_{42}Lys$ mutation ($V\kappa_{BCMA}$: $Gln_{42}Lys$); more preferably, the first heavy chain variable region of the first antigen-binding portion has a $Gln_{39}Glu$ mutation (VH_{BCMA}: $Gln_{39}Glu$).

7. The bispecific antibody or antigen-binding fragment thereof according to claim **6**, wherein the first light chain of the first antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 80 and 84; and/or the first heavy chain of the first antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 82 and 86;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 80; and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 82;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 84; and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 82;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 80; and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 86;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 84; and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 86;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 80, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 82, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 84, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 82, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 80, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 86, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 84, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 86, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

8. The bispecific antibody or antigen-binding fragment thereof according to claim **1**, wherein the first antigen is a GPC3 antigen;

preferably, the first light chain variable region of the first antigen-binding portion has $Gln_{43}Lys$ and $Gln_{39}Glu$ mutations ($V\kappa_{GPC3}$: $Gln_{43}Lys$; VH_{GPC3}: $Gln_{39}Glu$).

9. The bispecific antibody or antigen-binding fragment thereof according to claim **8**, wherein the first light chain of the first antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 88 and 92; and/or the first heavy chain of the first antigen-binding portion is selected from any of amino acid sequences of SEQ ID NOs: 90 and 94;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 88, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 90;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 92, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 94;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 88, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 90, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68;

preferably, the first light chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 92, and the first heavy chain of the first antigen-binding portion is the amino acid sequence of SEQ ID NO: 94, the second light chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 66, and the second heavy chain of the second antigen-binding portion is the amino acid sequence of SEQ ID NO: 68.

10. The bispecific antibody or antigen-binding fragment thereof according to claim **1**, wherein the Fc portion of the first antigen-binding portion and/or the second antigen-binding portion of the bispecific antibody adopts a knob-into-hole structure;

preferably, the human IgG4 knob-into-hole structure is used;

preferably, the first antigen-binding portion and/or the second antigen-binding portion of the bispecific antibody further has a $Ser_{228}Pro$ mutation, $Leu_{235}Glu$ mutation and/or $Pro_{329}Ala$ mutation.

11. A nucleic acid encoding the bispecific antibody or antigen-binding portion thereof according to claim **1**;

preferably, the second antigen-binding portion binds to a CD3 antigen, the nucleic acid encoding the second light chain variable region of the second antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 6, 11, 13, 17, 19 and 23; and/or the nucleic acid encoding the second heavy chain variable region of the second antigen-binding portion is selected from any of nucleotide sequences of ID NO: 25, 30, 33, 36, 39, 42, 45, 49, 51 and 53;

preferably, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from any of nucleotide sequences of ID NO: 59 and 67; and/or the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from any of nucleotide sequences of ID NO: 61 and 69; more preferably, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 59, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 61; more preferably, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69;

preferably, the first antigen-binding portion binds to the CD20 antigen, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 55, 63 and 71; and/or the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 57, 65 and 73; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 55, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 57; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 63, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 65; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 71, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 73;

preferably, the first antigen-binding portion binds to a BCMA antigen, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 81 and 85; and/or the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected

from SEQ ID NOs: 83 and 87; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 81, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 83;

more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 85, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 83; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 81, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 87; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 85, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 87;

preferably, the first antigen-binding portion binds to a GPC3 antigen, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 89 and 93; and/or the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from any of nucleotide sequences of SEQ ID NOs: 91 and 95; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 89, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 91; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 93, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 95;

more preferably, the first antigen-binding portion of the bispecific antibody binds the CD20 antigen, the second antigen binds the CD3 antigen, and the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 55, the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 57, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 59, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 61; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 63, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 65, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 59, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 61; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 71, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 73, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 63, and the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 65, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 59, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 61; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 55, the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 57, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69;

more preferably, the first antigen-binding portion of the bispecific antibody binds to the BCMA antigen, the second antigen binds to the CD3 antigen, and the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 81, the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 83, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 85, the nucleic acid encoding the first heavy chain of the first antigen-

binding portion is selected from the nucleotide sequence of SEQ ID NO: 83, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 81, the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 87, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 85, the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 87, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69;

more preferably, the first antigen-binding portion of the bispecific antibody binds to the GPC3 antigen, the second antigen binds to the CD3 antigen, and the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 89, the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 91, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69; more preferably, the nucleic acid encoding the first light chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 93, the nucleic acid encoding the first heavy chain of the first antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 95, the nucleic acid encoding the second light chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 67, and the nucleic acid encoding the second heavy chain of the second antigen-binding portion is selected from the nucleotide sequence of SEQ ID NO: 69.

12. A vector comprising the nucleic acid according to claim **11**.

13. A cell comprising the nucleic acid according to claim **11** or a vector comprising the nucleic acid.

14. A composition comprising the bispecific antibody or antigen-binding portion thereof according to claim **1**, a nucleic acid encoding the bispecific antibody or antigen-binding portion thereof, a vector comprising the nucleic acid and/or a cell comprising the nucleic acid or the vector.

15. An antibody-drug conjugate comprising the bispecific antibody or antigen-binding portion thereof according to claim **1** covalently attached to a therapeutic moiety;

preferably, the therapeutic moiety is selected from a cytotoxic moiety, a chemotherapeutic agent, a cytokine, an immunosuppressant, an immunostimulant, a lytic peptide, or a radioisotope;

preferably, the cytotoxic moiety is selected from: paclitaxel; cytochalasin B; gramicidin D; ethidium bromide; emetine; mitomycin; etoposide; teniposide; vincristine; vinblastine; colchicine; doxorubicin; daunorubicin; dihydroxy anthracenedione; tubulin inhibitors such as maytansine or analogs or derivatives thereof; antimitotic agents such as monomethyl auristatin E or F or analogues or derivatives thereof, hareotoxin 10 or 15 or an analogue thereof, irinotecan or an analog thereof, mitoxantrone; mithramycin; actinomycin D; 1-dehydrotestosterone; glucocorticoids; procaine; tetracaine; lidocaine; propranolol; puromycin; calicheamicin or an analogue or derivative thereof, antimetabolites such as methotrexate, 6 mercaptopurine, 6 thioguanine, cytarabine, fludarabine, 5 fluorouracil, decadiazine, hydroxyurea, asparaginase, gemcitabine or cladribine; alkylating agents such as mechlorethamine, thiopurine, chlorambucil, melphalan, BSNU, CCNU, cyclophosphamide, busulfan, dibromomannitol, streptozotocin, DTIC, procarbazine, mitomycin C; platinum derivatives such as cisplatin or carboplatin; duocarmycin A, duocarmycin SA, rapamycin (CC-1065) or analogs or derivatives thereof, antibiotics such as actinomycin, bleomycin, daunorubicin, doxorubicin, idarubicin, mithramycin, mitomycin, mitoxantrone, plicomycin, AMC; pyrrolo [2, 1-c] [1, 4]-benzodiazepine(PDB); diphtheria toxins and related molecules such as diphtheria A chain and active fragments and hybrid molecules thereof, ricin toxins such as ricin A or deglycosylated ricin A chain toxins, cholera toxins, shiga-like toxins such as SLT I, SLT II, SLT IIV, LT toxins, C3 toxins, shiga toxins, pertussis toxins, tetanus toxins, soybean Bowman-Birk protease inhibitors, *pseudomonas* exotoxin, arolin, saporin, modeccin, gelsolin, abrin A chain, modeccin A chain, α-sarcin, *Aleurites fordii* proteins, caryophyllin proteins, pokeweed proteins such as PAPI, PAPII and PAP-S, *Momordica charantia* inhibitors, curcin, crotin, *Sapaonaria officinalis* inhibitors, gelonin, mitomycin, restrictocin, phenomycin and enomycin toxins; RNase; DNase I, staphylococcal endotoxin A; pokeweed antiviral protein; diphtheria toxin and *pseudomonas* endotoxin;

preferably, the cytokine is selected from IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, IL-18, IL-23, IL-24, IL-27, IL-28a, IL-28b, IL-29, KGF, IFNa, IFN3, IFNy, GM-CSF, CD40L, Flt3 ligand, stem cell factor, ancestine and TNFa;

preferably, the radioisotope is selected from ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{67}Cu, ^{90}Y, ^{99}Tc, ^{125}, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At ^{212}Bi, ^{212}Pb, ^{213}Bi, ^{225} Ac and ^{227}Th.

16. A kit comprising the bispecific antibody or antigen-binding portion thereof according to claim **1**, or a nucleic acid encoding the bispecific antibody or antigen-binding portion thereof, or a vector comprising the nucleic acid, or a cell comprising the nucleic acid or the vector.

17. A method of diagnosing, treating or preventing diseases and conditions associated with a tumor antigen, wherein the method includes the steps of: administering to a subject a therapeutically effective amount of the bispecific antibody or antigen-binding fragment thereof according to claim **1** or a nucleic acid molecule encoding the bispecific antibody or antigen-binding portion thereof, or a vector or a cell comprising the nucleic acid, or a pharmaceutical composition;

wherein the pharmaceutical composition comprises any one of the bispecific antibody or antigen-binding fragment thereof, a nucleic acid encoding the bispecific antibody or antigen-binding portion thereof, a vector comprising the nucleic acid, and a cell comprising the nucleic acid or the vector;

preferably, the tumor antigen is CD20, the tumor antigen-related disease is a CD20-related disease; preferably, the CD20-related disease including B-cell diseases, such as B cell proliferative disorders, in particular CD20-positive B-cell disorders; preferably, the disease is selected from non-Hodgkin's lymphoma (NHL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and multiple myeloma (MM) and Hodgkin's lymphoma (HL);

preferably, the tumor antigen is BCMA, the tumor antigen-related disease is a BCMA-related disease; preferably, the BCMA-related disease including B-cell disease; preferably, the disease is cancer; more preferably, the cancer is a B-cell related cancer selected from multiple myeloma, malignant plasmacytoma, hodgkin's lymphoma, nodular lymphocyte-predominant Hodgkin's lymphoma, Kahler's disease and myeloid leukemia, plasma cell leukemia, plasmacytoma, B-cell prolymphocytic leukemia, hairy cell leukemia, B-cell non-Hodgkin's lymphoma (NHL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), follicular lymphoma, burkitt lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, precursor B-lymphocyte lymphoma, myeloid leukemia, waldenstrom's macroglobulinemia, diffuse large B cell lymphoma, follicular lymphoma, marginal zone lymphoma, mucosa-related lymphoid tissue lymphoma, small cell lymphocytic lymphoma, mantle cell lymphoma, burkitt lymphoma, primary mediastinal (thymic) large B cell lymphoma, lymphoplasmacytic lymphoma, waldenstrom's macroglobulinemia, lymph node marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, large B-cell lymphoma rich in T-cells/histiocytes, primary central nervous system lymphoma, primary cutaneous diffuse large B-cell lymphoma (leg type), elderly EBV-positive diffuse large B-cell lymphoma, inflammation-related diffuse large B-cell lymphoma, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablast-cell lymphoma, large B-cell lymphoma arising in HHV8-related multicenter Castleman's disease, unclassified B-cell lymphoma with intermediate features between diffuse large B-cell lymphoma and Burkitt's lymphoma, unclassified B-cell lymphoma with intermediate features between diffuse large B-cell lymphoma and classic Hodgkin's lymphoma, and other B-cell-related lymphomas; more preferably, the B-cell disease is a B-cell disorder;

preferably, the plasma cell disorder is selected from: multiple myeloma, plasmacytoma, plasma cell leukemia, macroglobulinemia, amyloidosis, waldenstrom's macroglobulinemia, solitary plasmacytoma of the bone, extramedullary plasmacytoma, osteosclerotic myeloma, heavy chain disease, monoclonal gammopathy of unclear significance, and multiple myeloma of stasis type;

preferably, the disease is an autoimmune disorder such as systemic lupus erythematosus or rheumatoid arthritis;

preferably, the tumor antigen is GPC3, the tumor antigen-related disease is a GPC3-related disease; preferably, the GPC3-related disease includes tumors; preferably, the tumor is a cancer;

more preferably, the cancer is a GPC3-positive cancer, which, for example, can be a GPC3-positive liver cancer, a GPC3-positive hepatocellular carcinoma, a GPC3-positive pancreatic cancer, a GPC3-positive lung cancer, a GPC3-positive colon cancer, a GPC3-positive breast cancer, a GPC3-positive prostate cancer, a GPC3-positive leukemia, or a GPC3-positive lymphoma.

18. A kit comprising the composition according to claim **14**.

19. A kit comprising the antibody-drug conjugate according to claim **15**.

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