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(54) **ANTI-CD3 ANTIBODY VARIANT, FUSION PROTEIN, AND APPLICATION**

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§ 371 (c)(1),
(2) Date: **Dec. 4, 2023**

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C07K 14/54	(2006.01)
C07K 14/715	(2006.01)

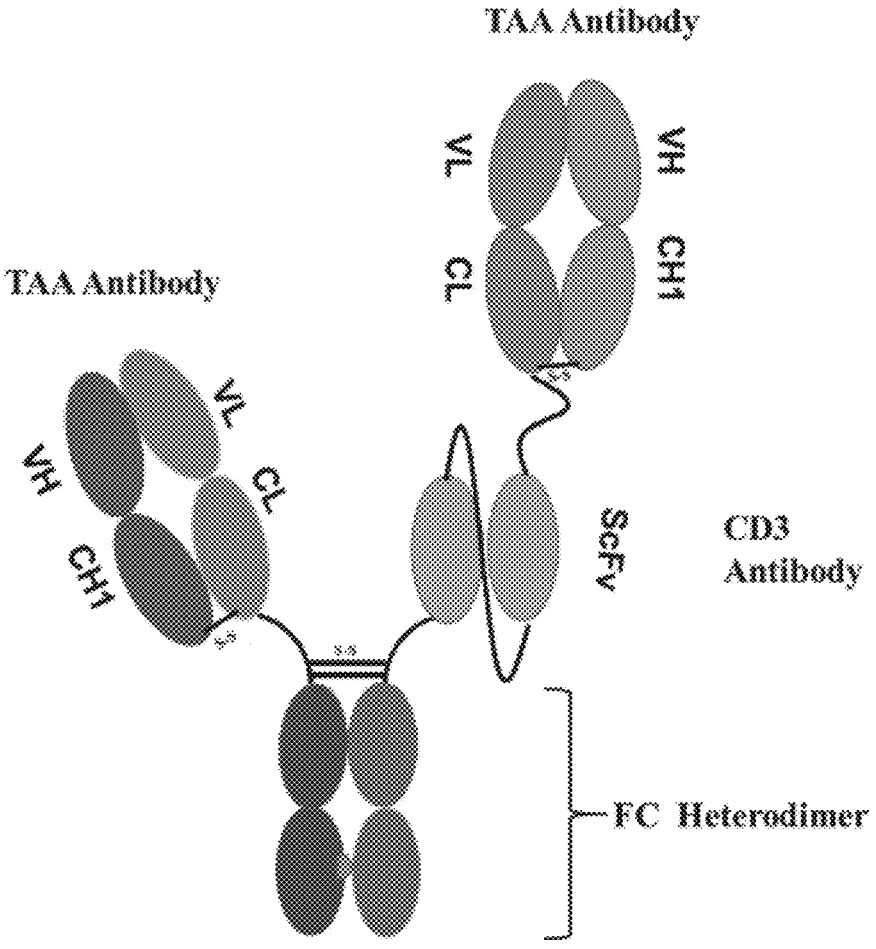
(52) **U.S. Cl.**

CPC ***C07K 16/2809*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 14/4748*** (2013.01); ***C07K 14/5443*** (2013.01); ***C07K 14/7155*** (2013.01); *A61K 2039/505* (2013.01); *C07K 2317/24* (2013.01); *C07K 2317/31* (2013.01); *C07K 2317/52* (2013.01); *C07K 2317/565* (2013.01); *C07K 2317/622* (2013.01); *C07K 2319/00* (2013.01)

(57) **ABSTRACT**

Provided are an anti-CD3 antibody variant, a fusion protein, and an application. An anti-CD3 antibody is mutated to obtain a variant thereof. The provided fusion protein comprises: (1) an anti-tumor-associated antigen (TAA)/anti-CD3 bispecific antibody; (2) anti-TAA, anti-CD3 and IL15/IL15Ra-containing multifunctional fusion proteins; and (3) anti-TAA and IL15/IL15Ra-containing fusion proteins. Further provided are a nucleic acid molecule encoding an antibody molecule and a vector, and a pharmaceutical use of the antibody molecule.

Specification includes a Sequence Listing.



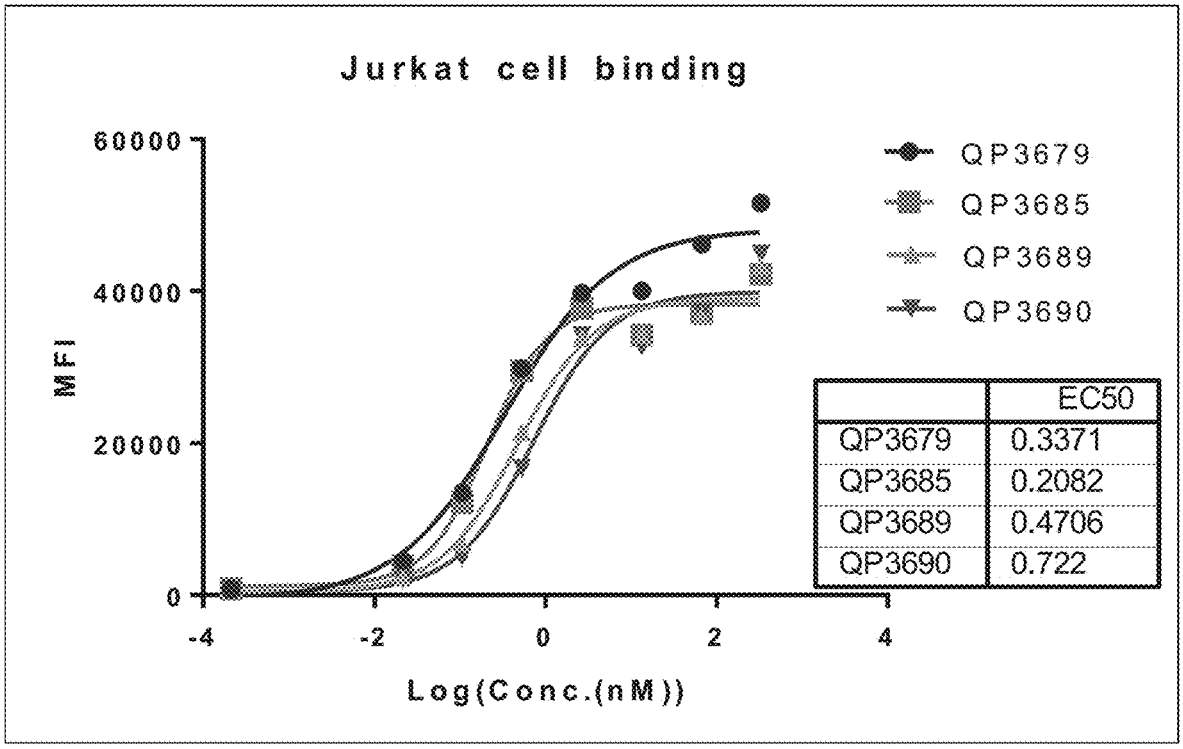

Jurkat cell binding
60000
40000
20000
0
MFI
-4
-2
0
2
4
Log(Conc.(nM))
QP3679
QP3685
QP3689
QP3690
EC50
QP3679 0.3371
QP3685 0.2082
QP3689 0.4706
QP3690 0.722

FIG. 1

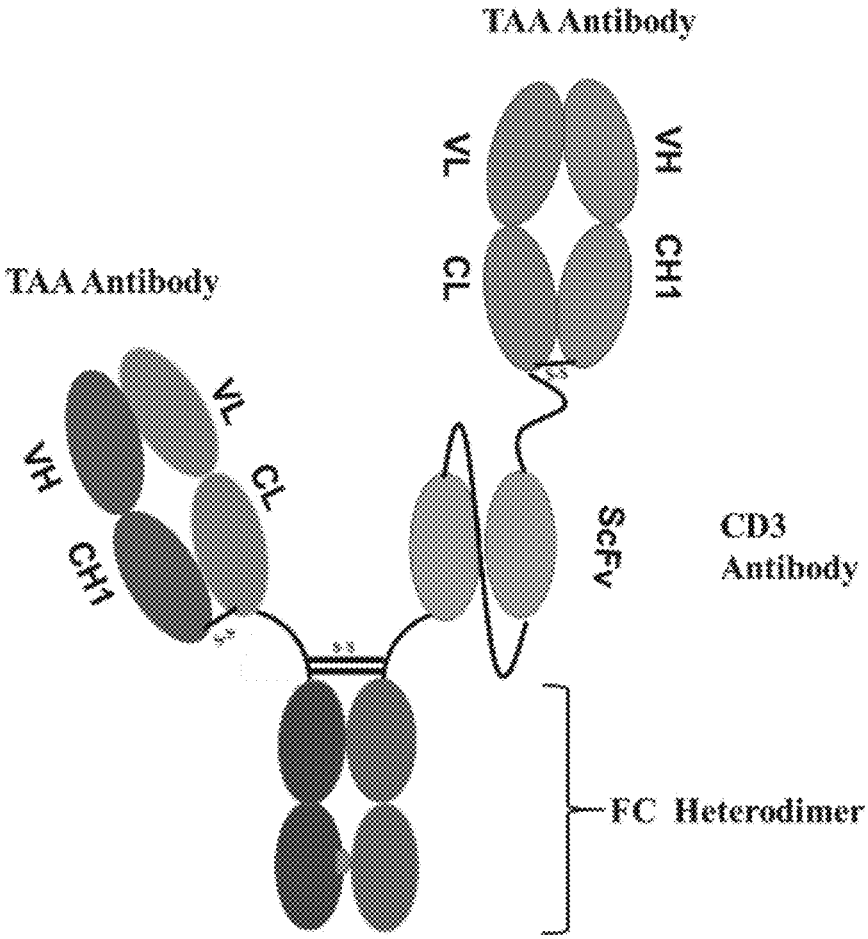

TAA Antibody
VL
VH
CL
CH1
TAA Antibody
VL
VH
CL
CH1
ScFv
CD3
Antibody
FC Heterodimer

FIG. 2

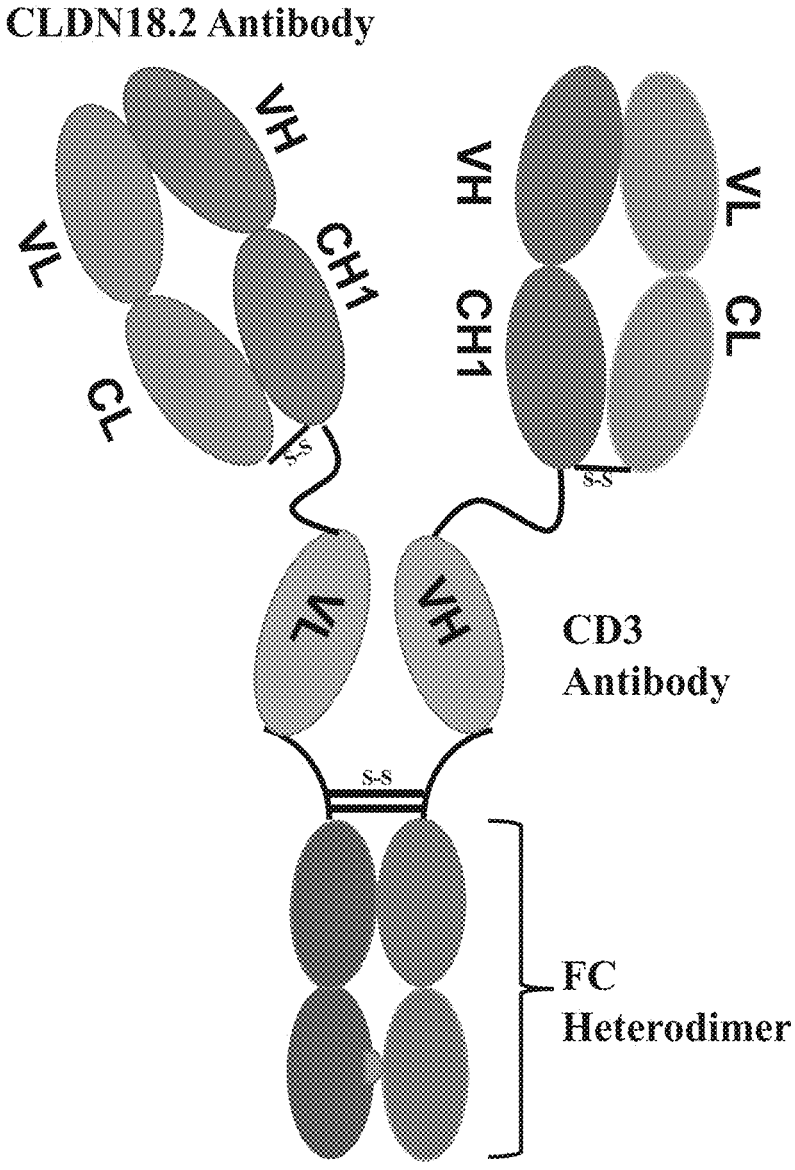

CLDN18.2 Antibody
VH
VL
CH1
CL
S-S
VH
VL
CH1
CL
S-S
VL
VH
CD3
Antibody
S-S
FC
Heterodimer

FIG. 3

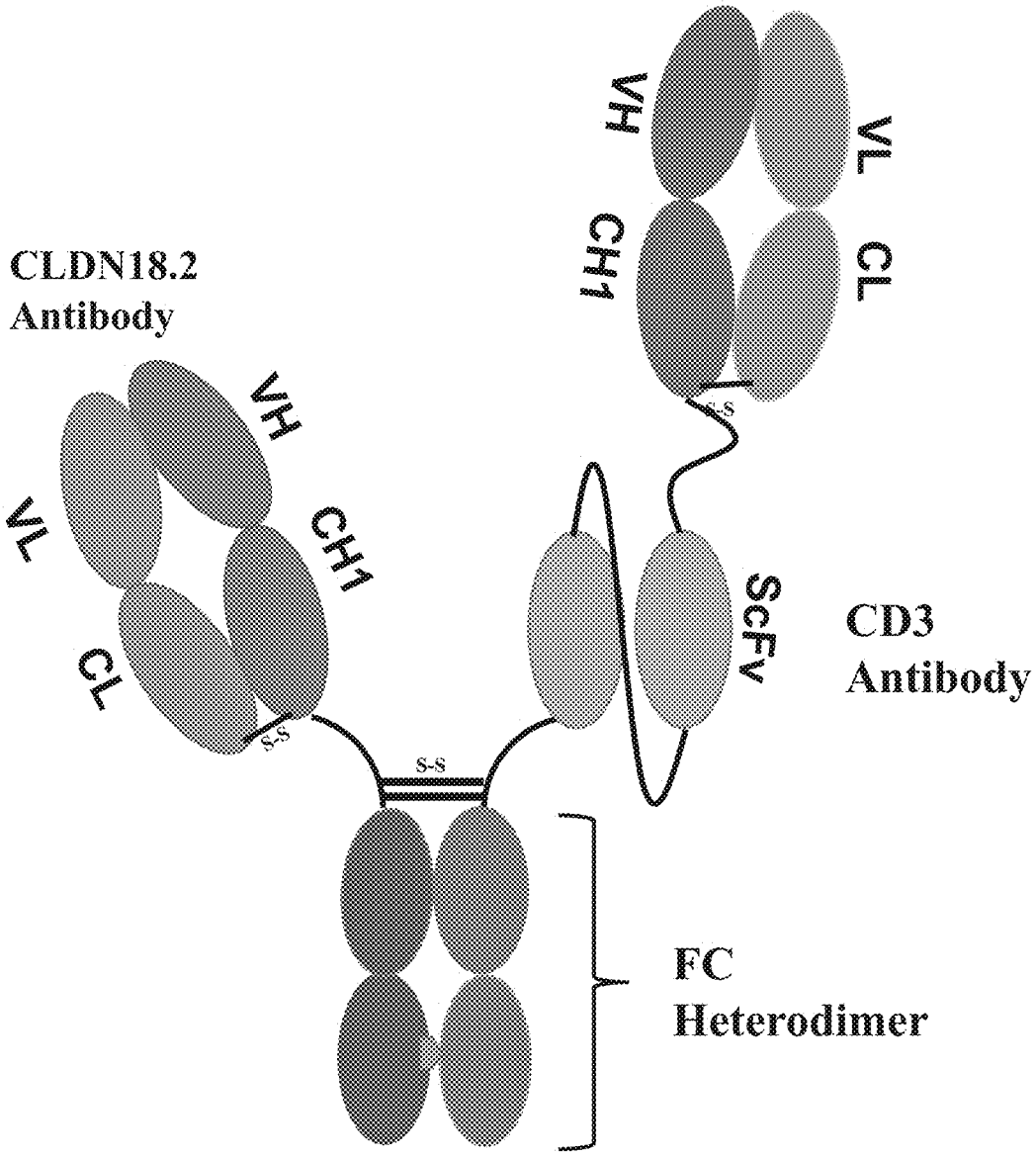
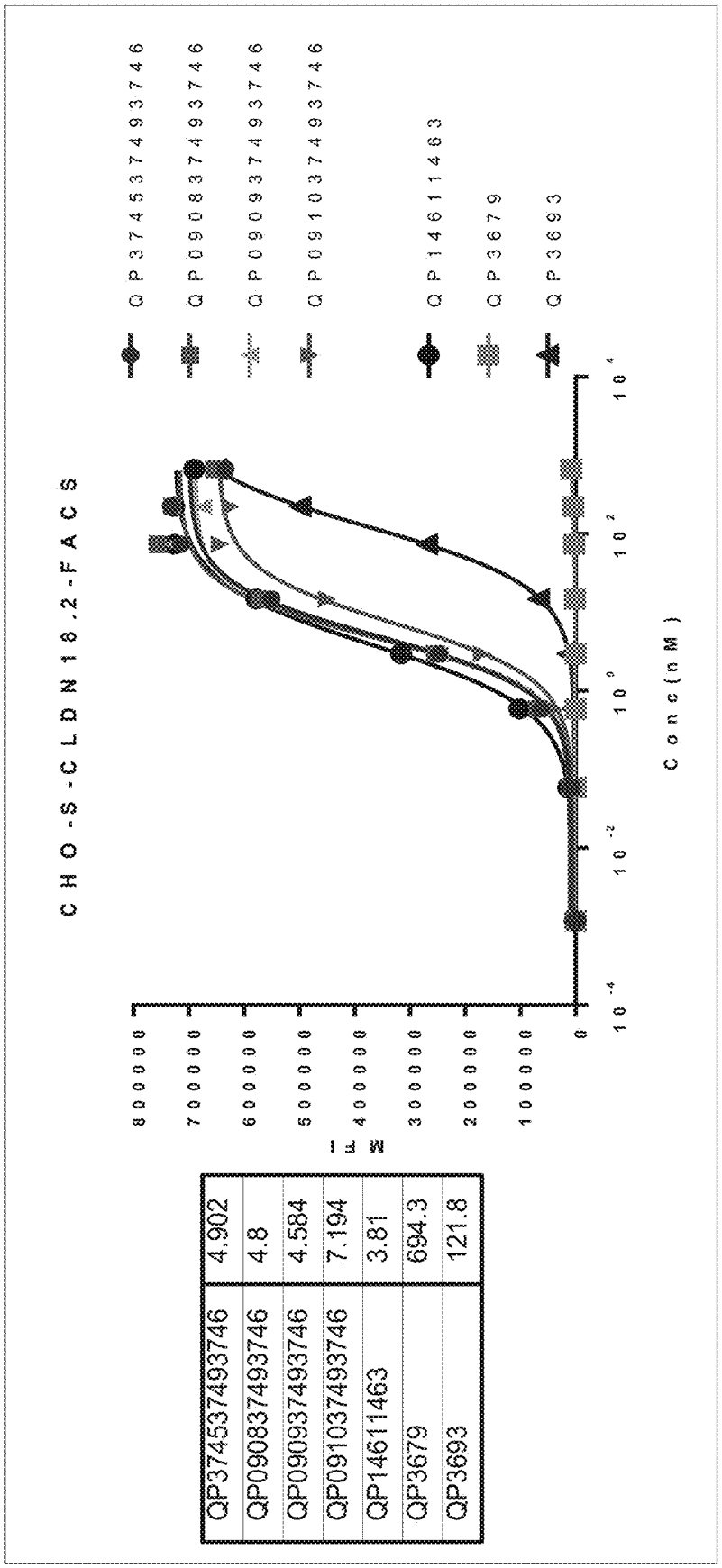

CLDN18.2
Antibody
VH
VL
CH1
CL
S-S
S-S
S-S
VH
VL
CH1
CL
ScFv
CD3
Antibody
FC
Heterodimer

FIG. 4



QP37453749337746	4.902
QP09083749337746	4.8
QP09093749337746	4.584
QP09103749337746	7.194
QP14611463	3.81
QP3679	694.3
QP3693	121.8

FIG. 5

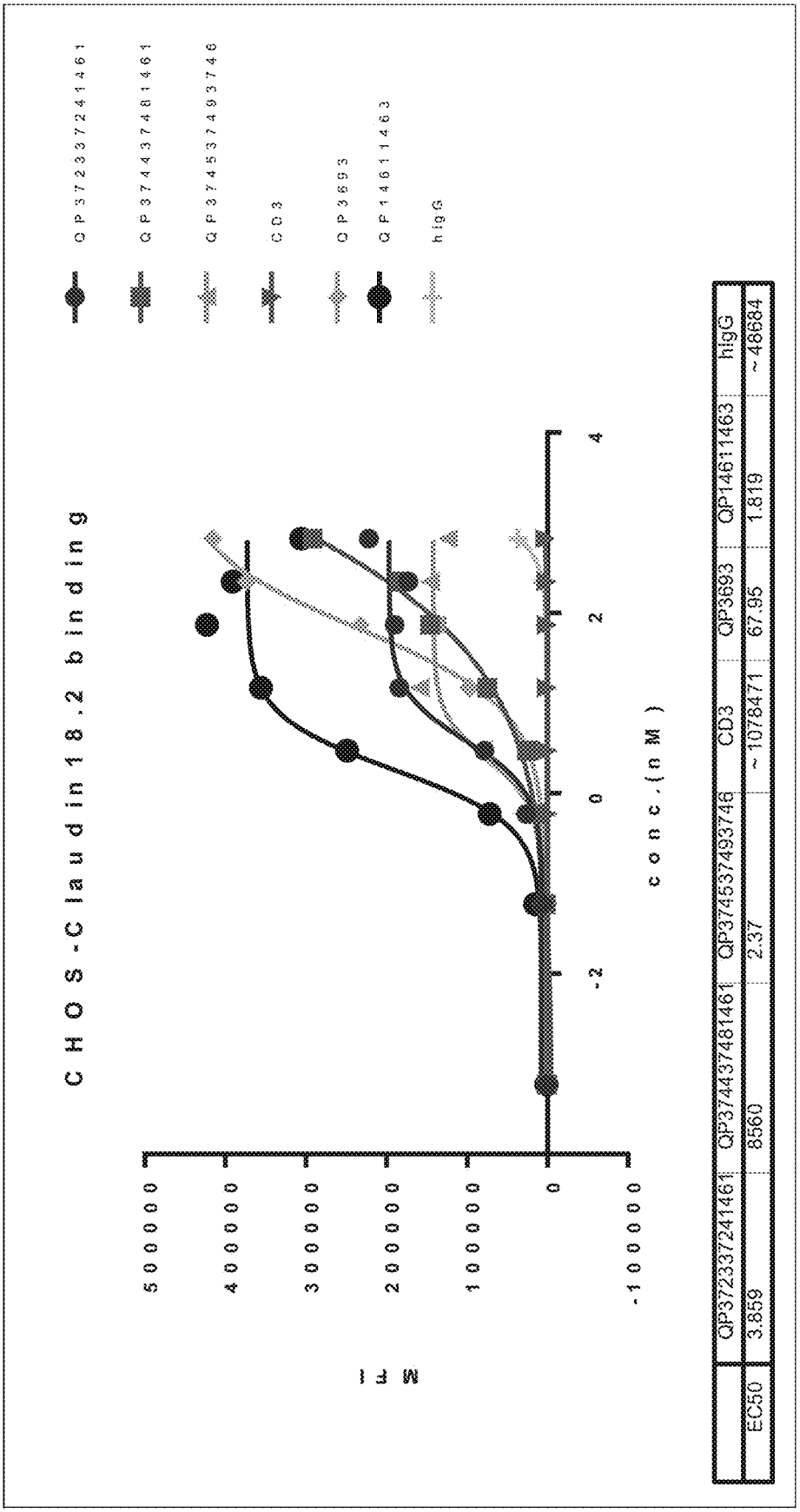
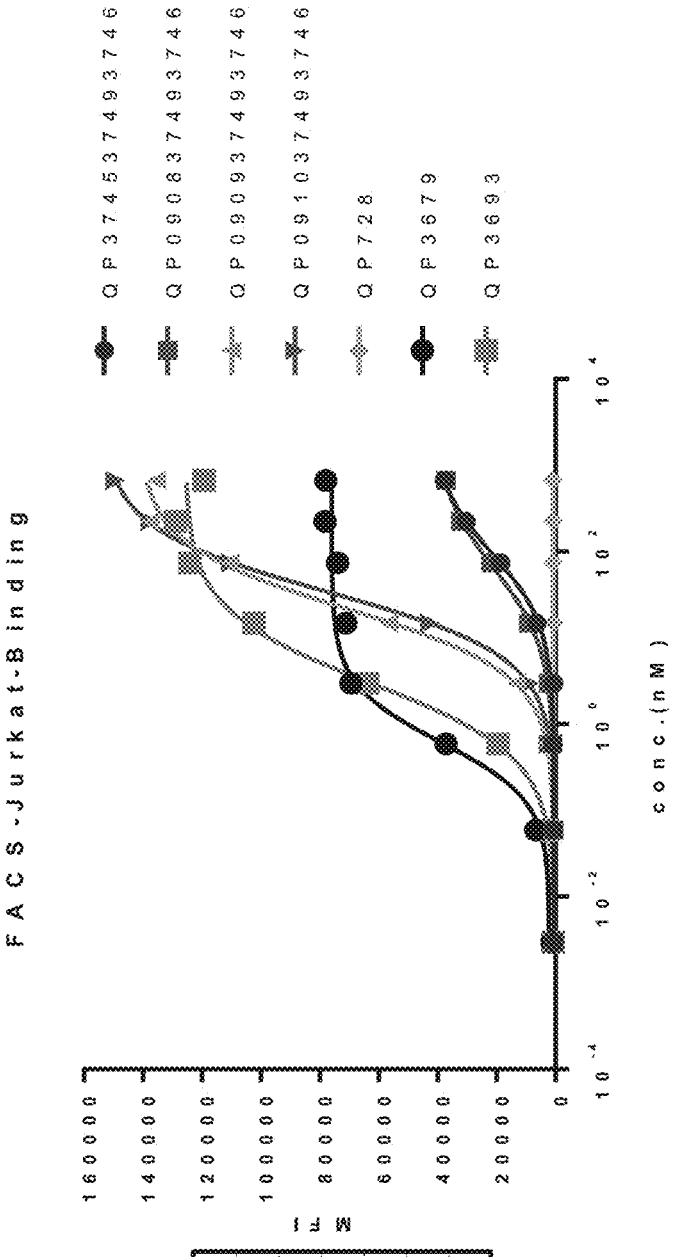
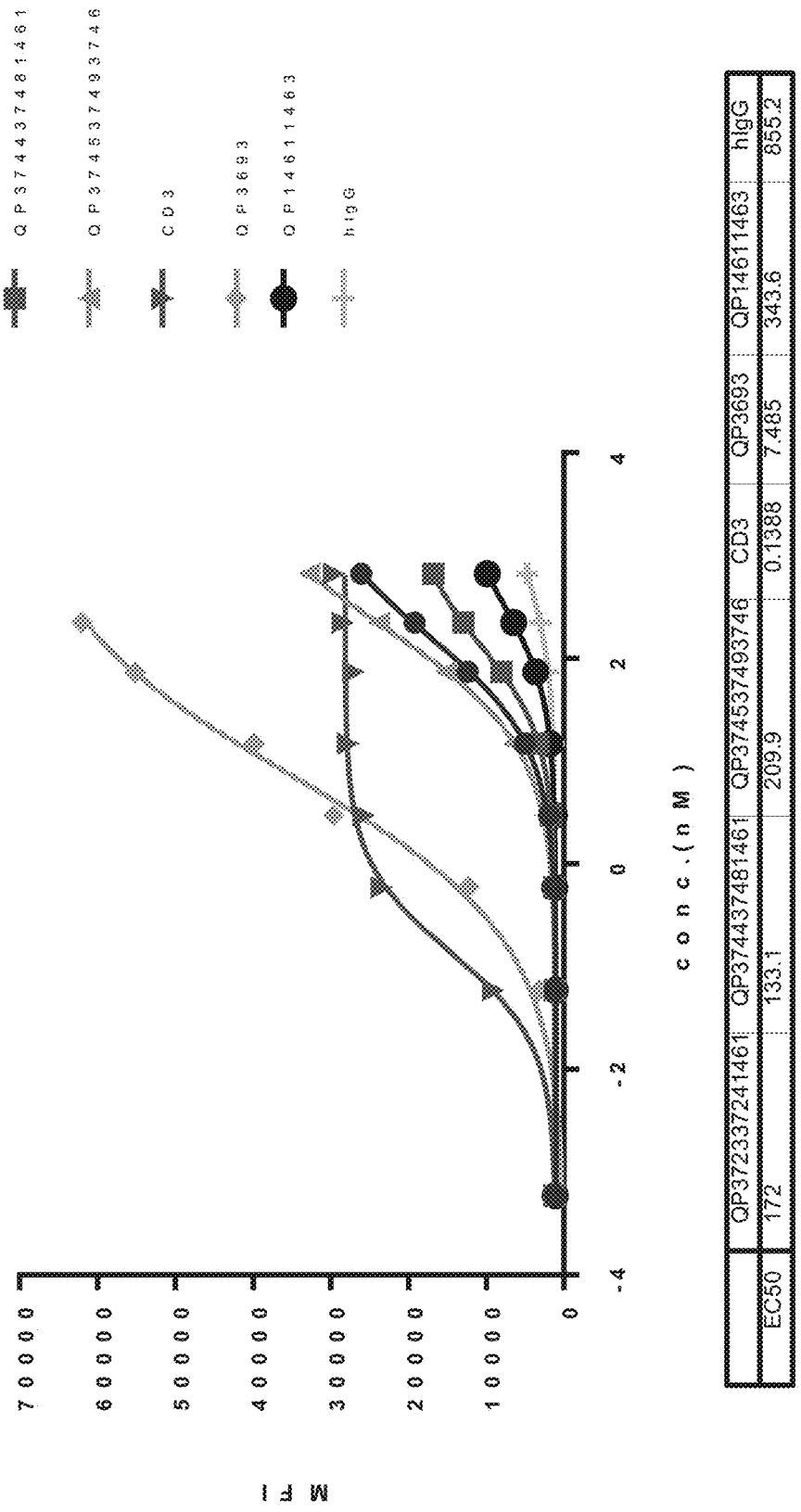

CHOS-Claudin18.2 binding
QP3723372414461
QP3744374814461
QP3745374937461
CD3
QP3693
QP14611463
hIgG
MFI
conc.(nM)
5000000
4000000
3000000
2000000
1000000
0
-1000000
-2
0
2
4
QP3723372414461 QP3744374814461 QP3745374937461 CD3 QP3693 QP14611463 hIgG
EC50 3.859 8560 2.37 ~1078471 67.95 1.819 ~48684

FIG. 6



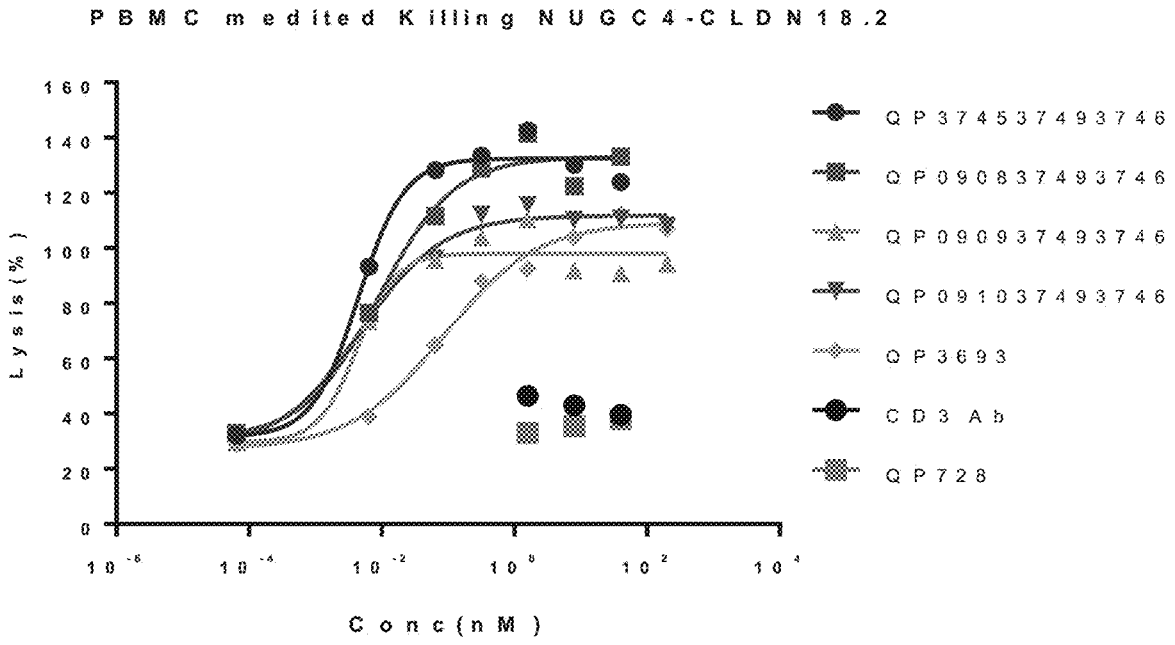
QP374537493746	96.39
QP090837493746	64.34
QP090937493746	21.89
QP091037493746	33.95
QP728	~1079
QP3679	0.6194
QP3693	3.034

FIG. 7



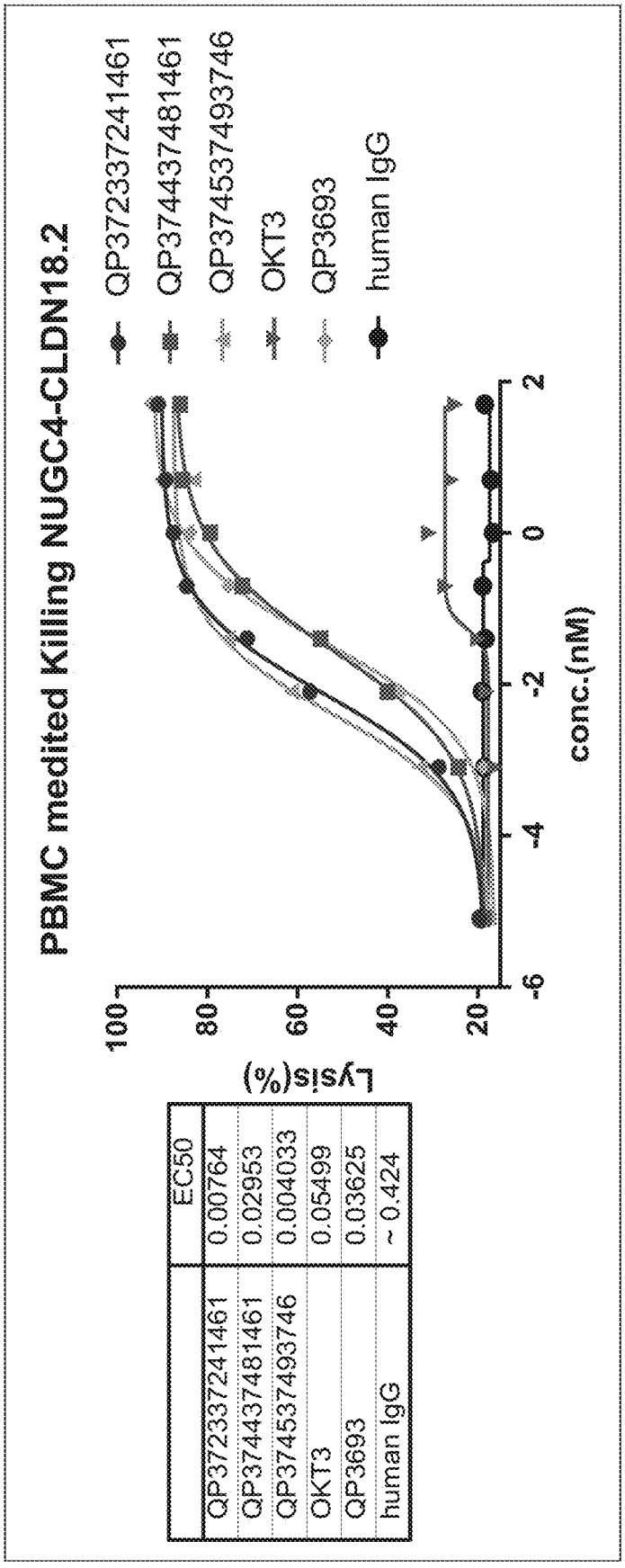
	QP372337241461	QP374437481461	QP374537493746	CD3	QP3693	QP14611463	hIgG
EC50	172	133.1	209.9	0.1388	7.485	343.6	855.2

FIG. 8



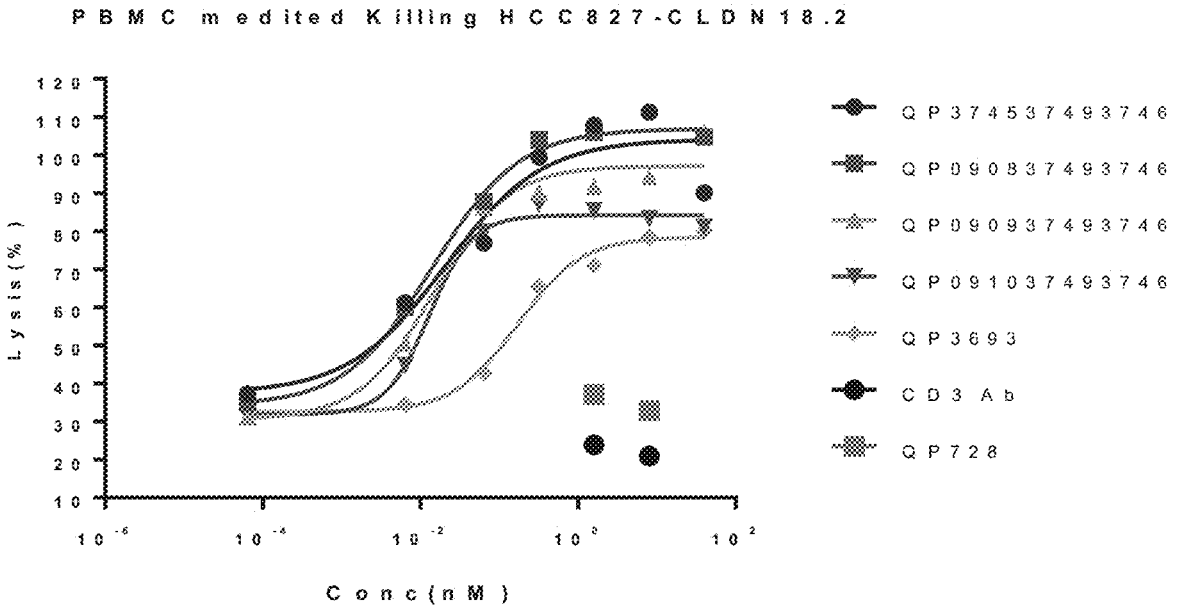
QP374537493746	0.004473
QP090837493746	0.008899
QP090937493746	0.004283
QP091037493746	0.00472
QP3693	0.08622
CD3 Ab	

FIG. 9



	EC50
QP372337241461	0.00764
QP374437481461	0.02953
QP374537493746	0.004033
OKT3	0.05499
QP3693	0.03625
human IgG	~ 0.424

FIG. 10



QP374537493746	0.02061
QP090837493746	0.01426
QP090937493746	0.01477
QP091037493746	0.01298
QP3693	0.1722
CD3 Ab	
QP728	

FIG. 11

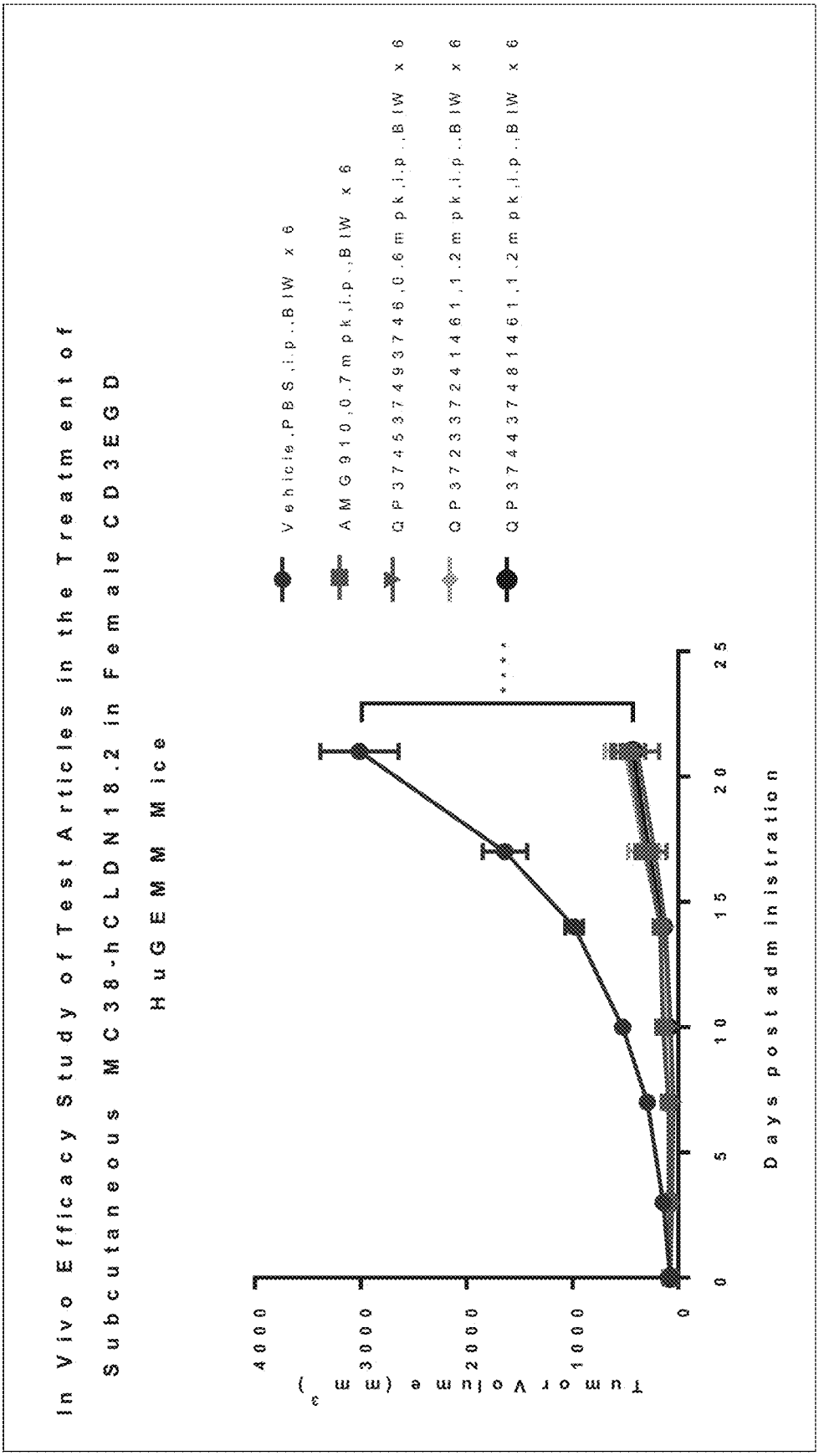

In Vivo Efficacy Study of Test Articles in the Treatment of
Subcutaneous MC38-hCLDN18.2 in Female CD3EGD
HuGEMM Mice
Vehicle,PBS,i.p.,BIW x 6
AMG910,0.7mpk,i.p.,BIW x 6
QP3745374937746,0.6mpk,i.p.,BIW x 6
QP3723372414611,1.2mpk,i.p.,BIW x 6
QP3744374814611,1.2mpk,i.p.,BIW x 6
****
Tumor Volume (mm3)
4000
3000
2000
1000
0
0
5
10
15
20
25
Days postadministration

FIG. 12

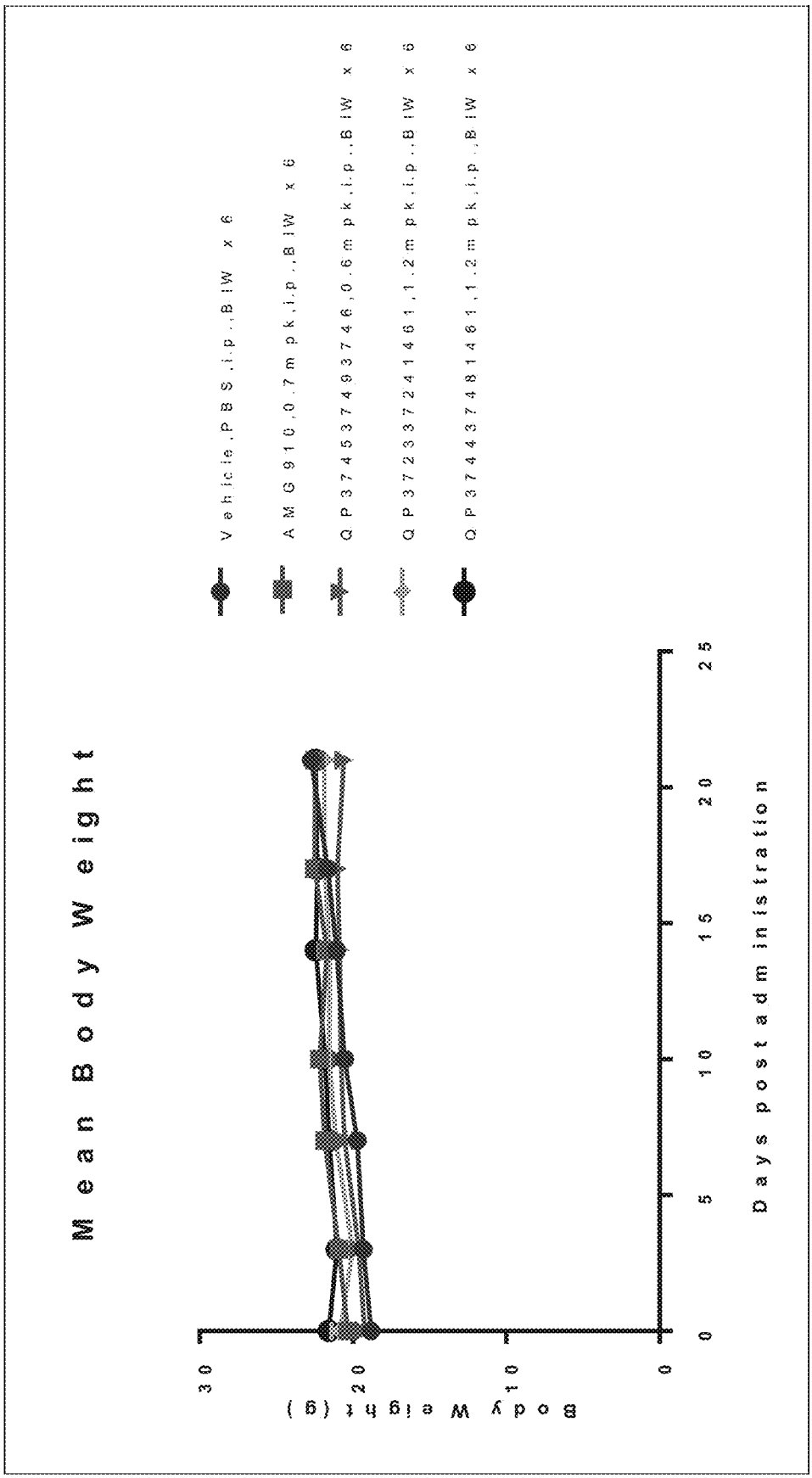

Mean Body Weight
Vehicle,PBS,i.p.,BIW x 6
AMG 910,0.7mpk,i.p.,BIW x 6
QP3745374937746,0.6mpk,i.p.,BIW x 6
QP3723372411461,1.2mpk,i.p.,BIW x 6
QP3744374814461,1.2mpk,i.p.,BIW x 6
Body weight (g)
30
20
10
0
0
5
10
15
20
25
Days post administration

FIG. 13

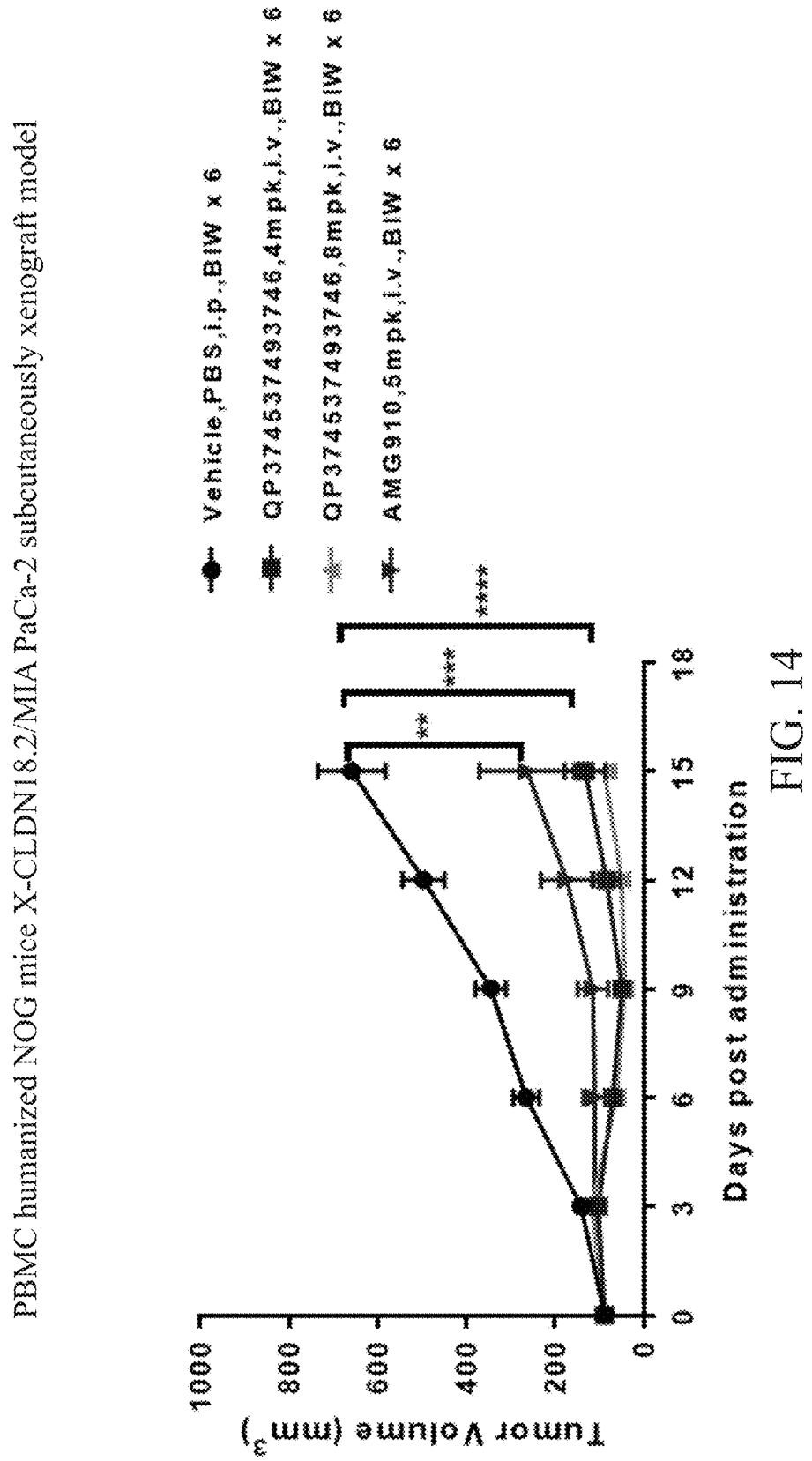

PBMC humanized NOG mice X-CLDN18.2/MIA PaCa-2 subcutaneously xenograft model
Vehicle,PBS,i.p.,BIW x 6
QP3745374937 46,4mpk,i.v.,BIW x 6
QP3745374937 46,8mpk,i.v.,BIW x 6
AMG910,5mpk,i.v.,BIW x 6
Tumor Volume (mm3)
1000
800
600
400
200
0
0
3
6
9
12
15
18
Days post administration
**
***
****

FIG. 14

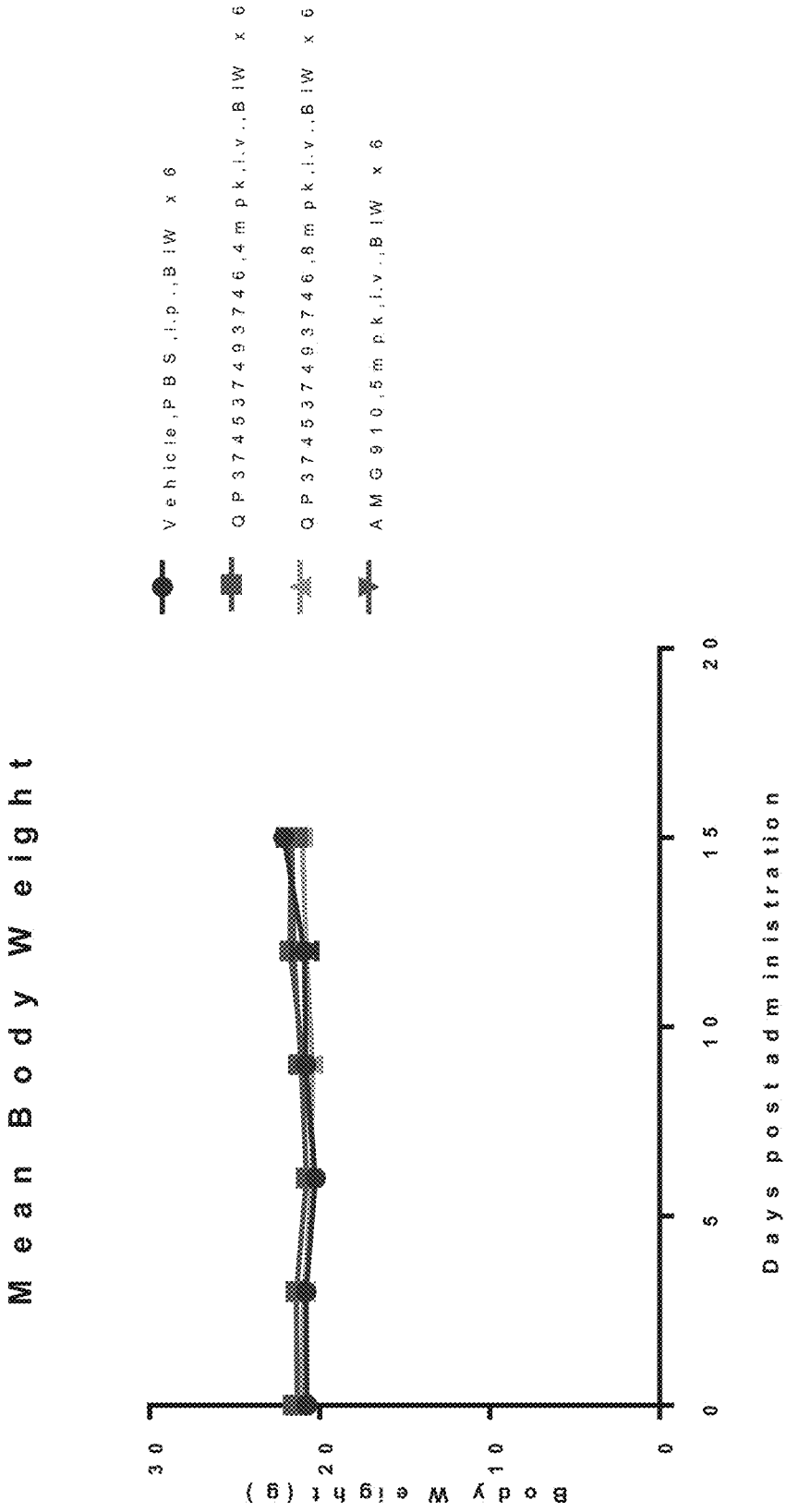

Mean Body Weight
Body weight (g)
0
10
20
30
0
5
10
15
20
Days post administration
Vehicle,PBS,i.p.,BIW x 6
QP3745374937746,4mpk,i.v.,BIW x 6
QP3745374937746,8mpk,i.v.,BIW x 6
AMG910,5mpk,i.v.,BIW x 6

FIG. 15

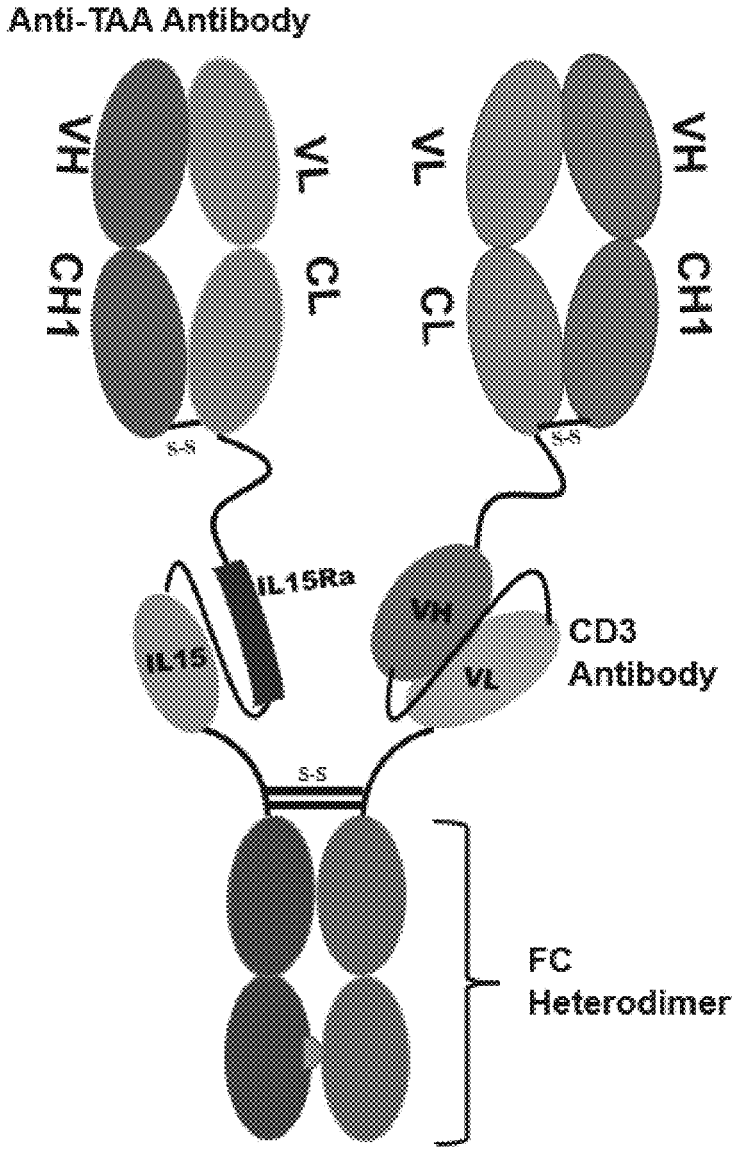

Anti-TAA Antibody
VH
VL
CH1
CL
VL
VH
CL
CH1
S-S
S-S
IL15Ra
IL15
VH
VL
CD3
Antibody
S-S
FC
Heterodimer

FIG. 16

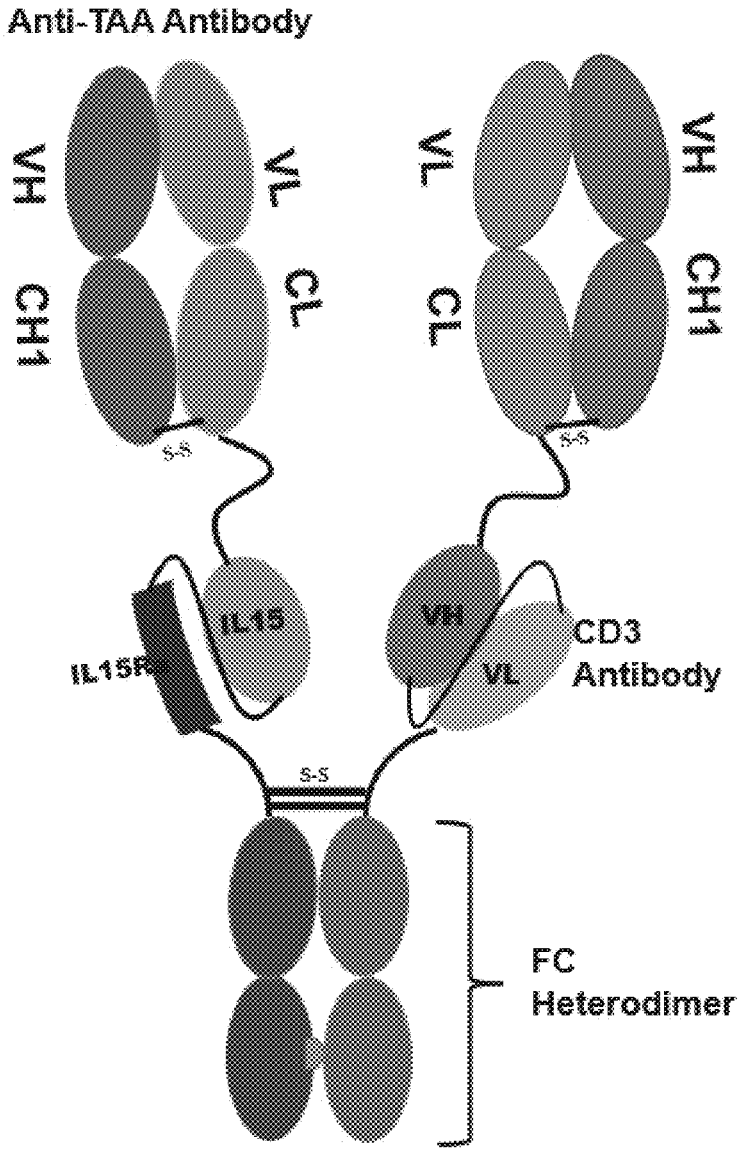

Anti-TAA Antibody
VH
VL
CH1
CL
S-S
VL
VH
CL
CH1
S-S
IL15
IL15R
VH
VL
CD3
Antibody
S-S
FC
Heterodimer

FIG. 17

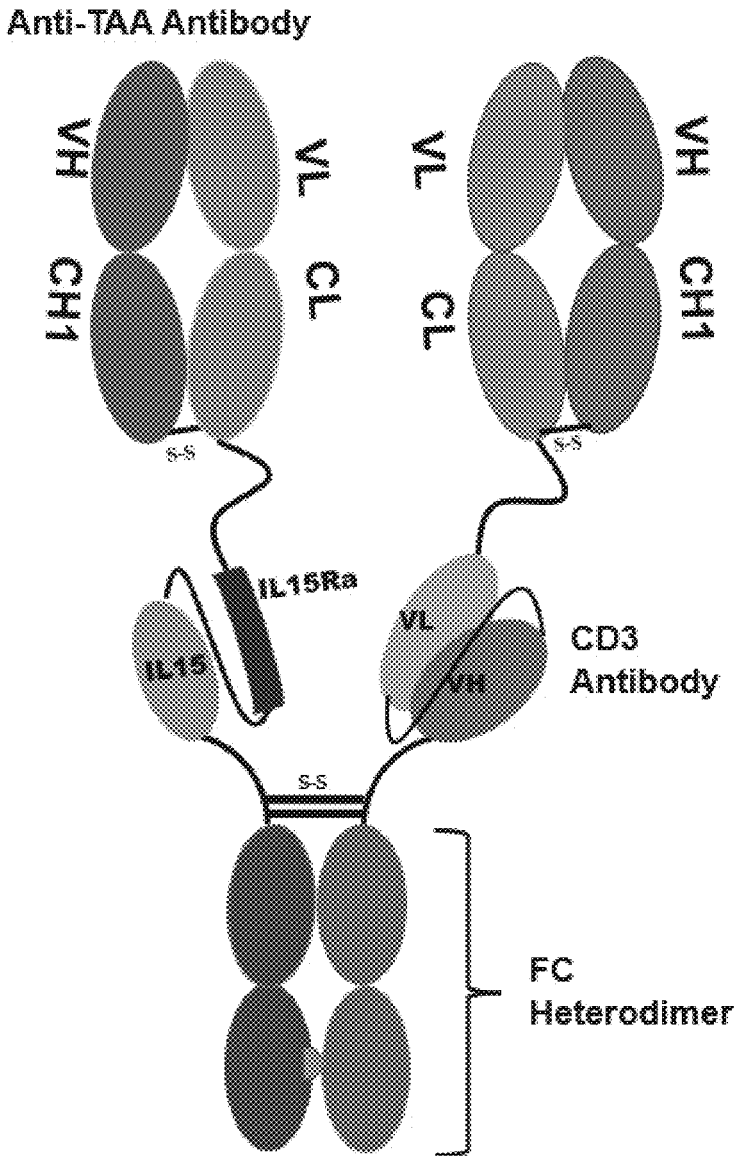

Anti-TAA Antibody
VH
VL
CH1
CL
VL
VH
CL
CH1
S-S
S-S
IL15Ra
IL15
VL
VH
CD3
Antibody
S-S
FC
Heterodimer

FIG. 18

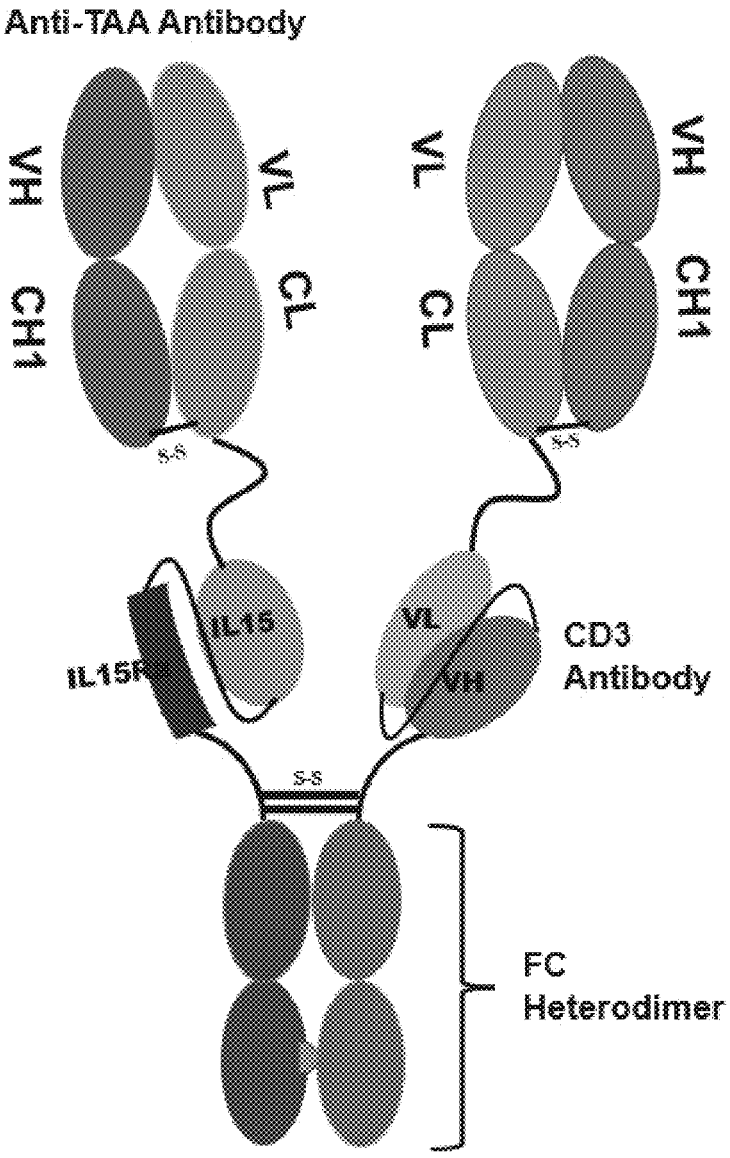

Anti-TAA Antibody
VH
VL
CH1
CL
S-S
VL
VH
CL
CH1
S-S
IL15
IL15R
VL
VH
CD3
Antibody
S-S
FC
Heterodimer

FIG. 19

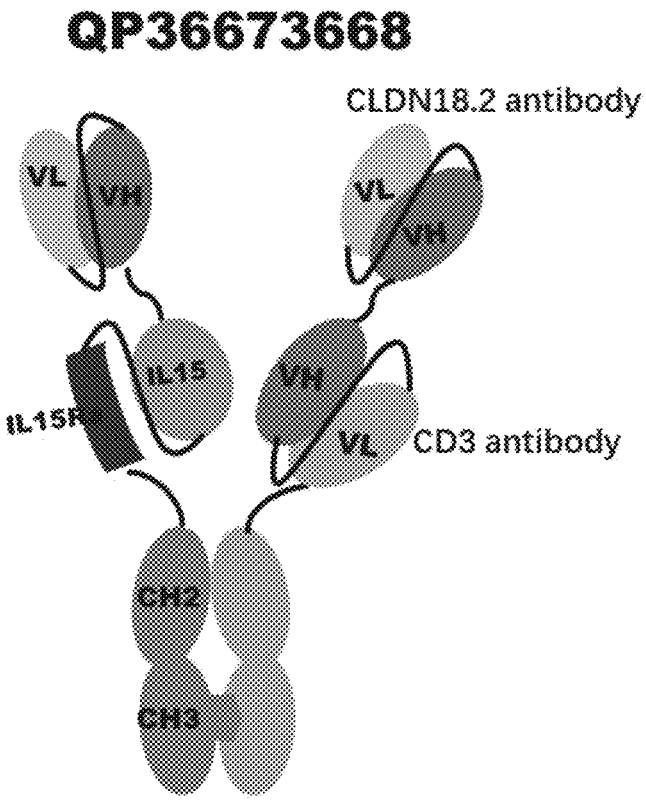

QP36673668
CLDN18.2 antibody
VL
VH
VL
VH
IL15
IL15R
VH
VL
CD3 antibody
CH2
CH3

FIG. 20

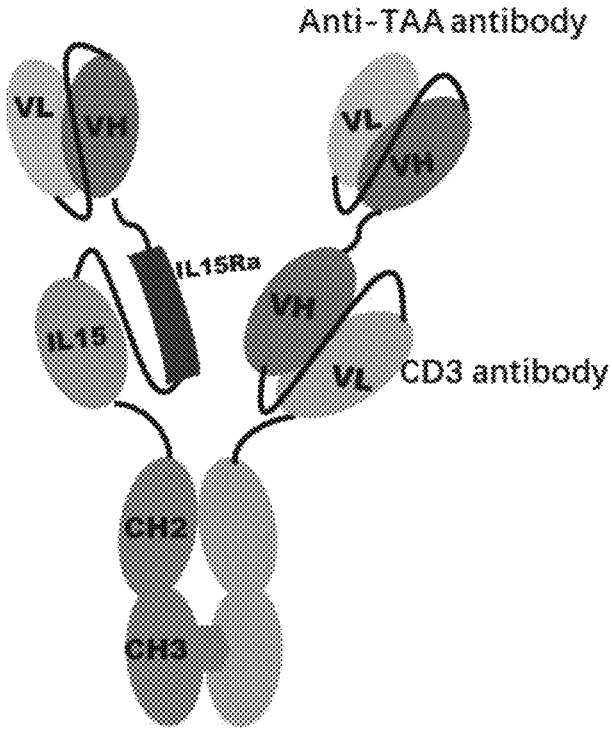

Anti-TAA antibody
VL
VH
VL
VH
IL15Rα
IL15
VH
VL
CD3 antibody
CH2
CH3

FIG. 21

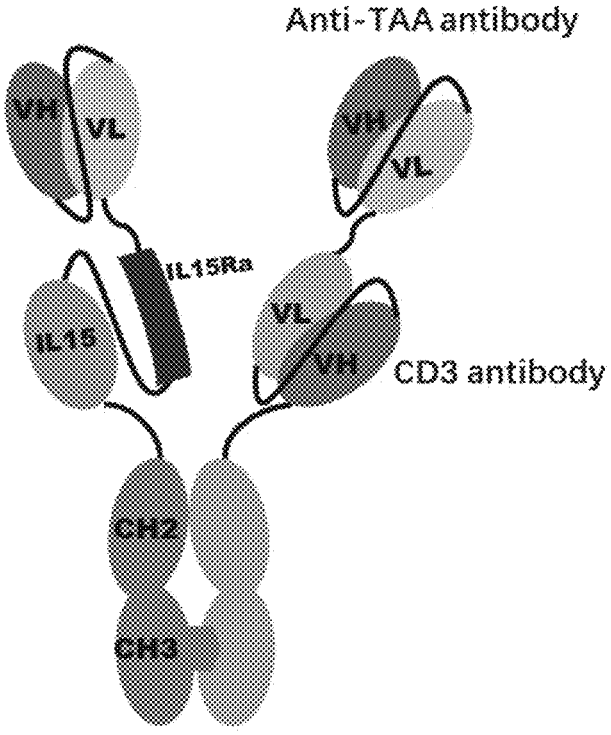

Anti-TAA antibody
VH
VL
VH
VL
IL15Ra
IL15
VL
VH
CD3 antibody
CH2
CH3

FIG. 22

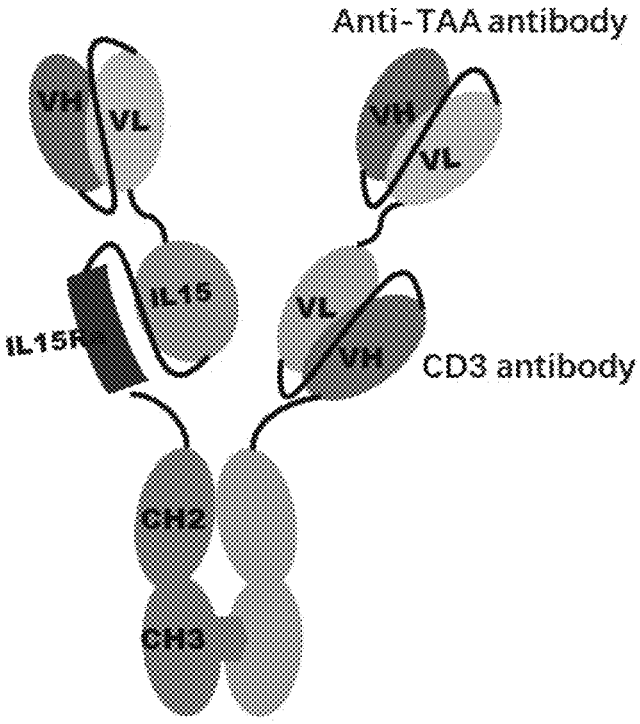

Anti-TAA antibody
VH
VL
VH
VL
IL15
IL15R
VL
VH
CD3 antibody
CH2
CH3

FIG. 23

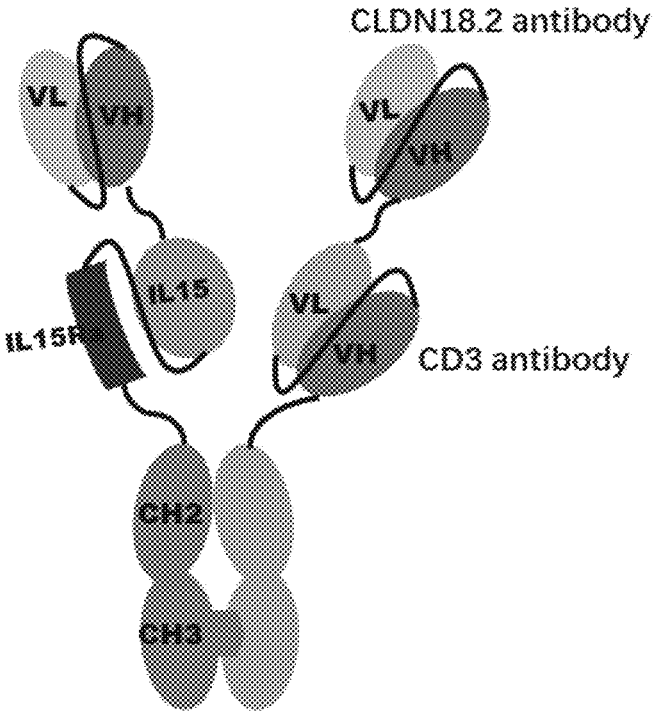

CLDN18.2 antibody
VL
VH
VL
VH
IL15
IL15R
VL
VH
CD3 antibody
CH2
CH3

FIG. 24

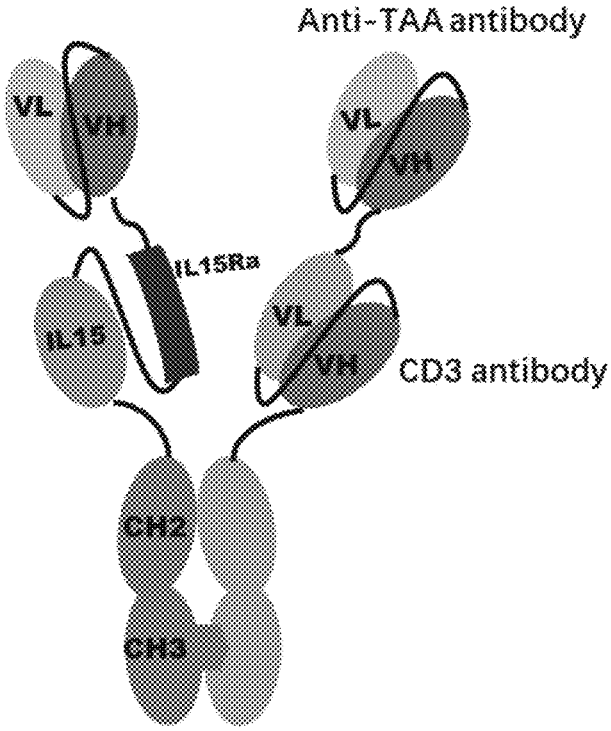

Anti-TAA antibody
VL
VH
VL
VH
IL15Rα
IL15
VL
VH
CD3 antibody
CH2
CH3

FIG. 25

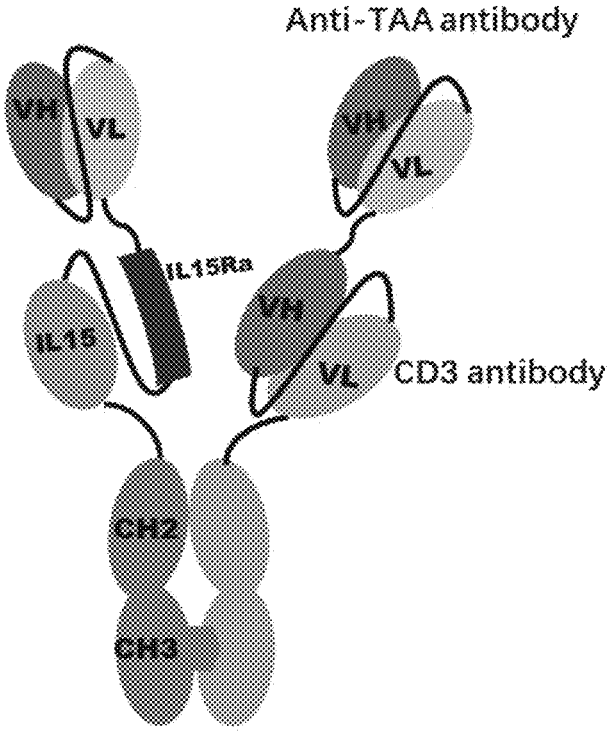

Anti-TAA antibody
VH
VL
VH
VL
IL15Ra
IL15
VH
VL
CD3 antibody
CH2
CH3

FIG. 26

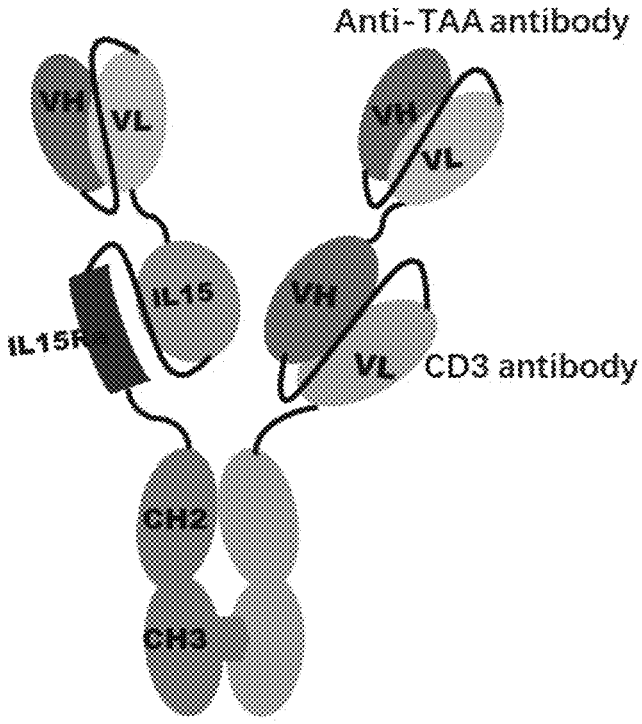

Anti-TAA antibody
VH
VL
VH
VL
IL15
IL15R
VH
VL
CD3 antibody
CH2
CH3

FIG. 27

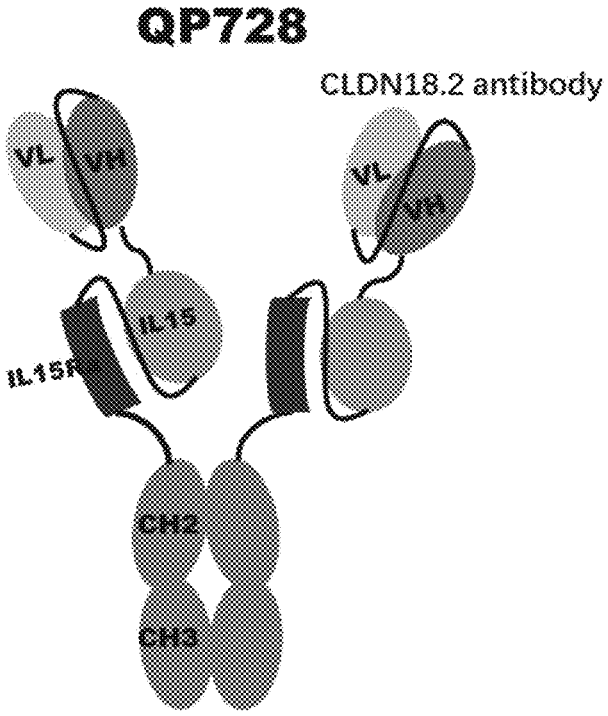
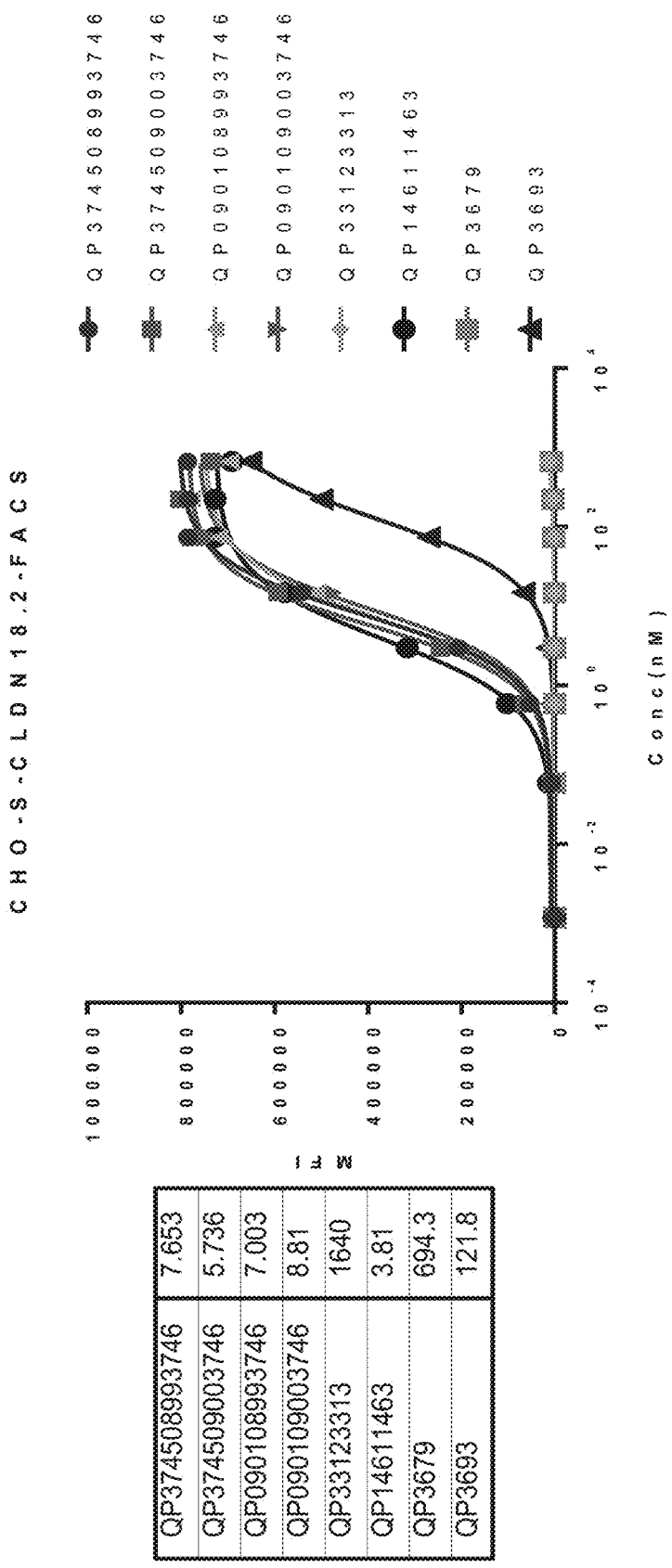


FIG. 28



QP37450899374 6	7.653
QP37450900374 6	5.736
QP09010899374 6	7.003
QP09010900374 6	8.81
QP33123313	1640
QP14611463	3.81
QP3679	694.3
QP3693	121.8

FIG. 29

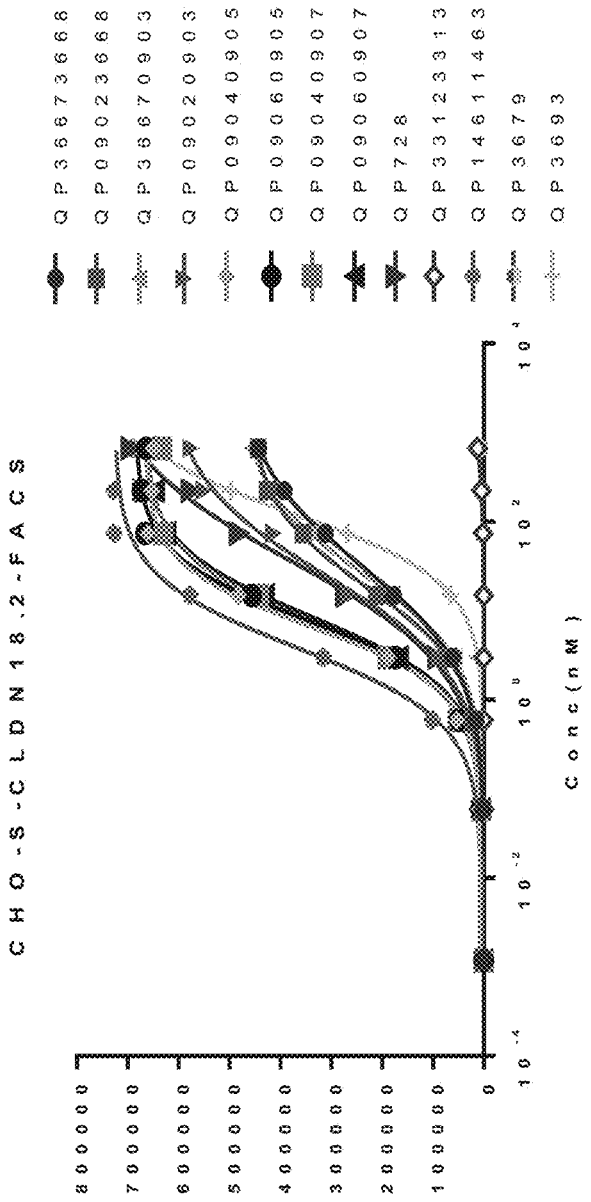
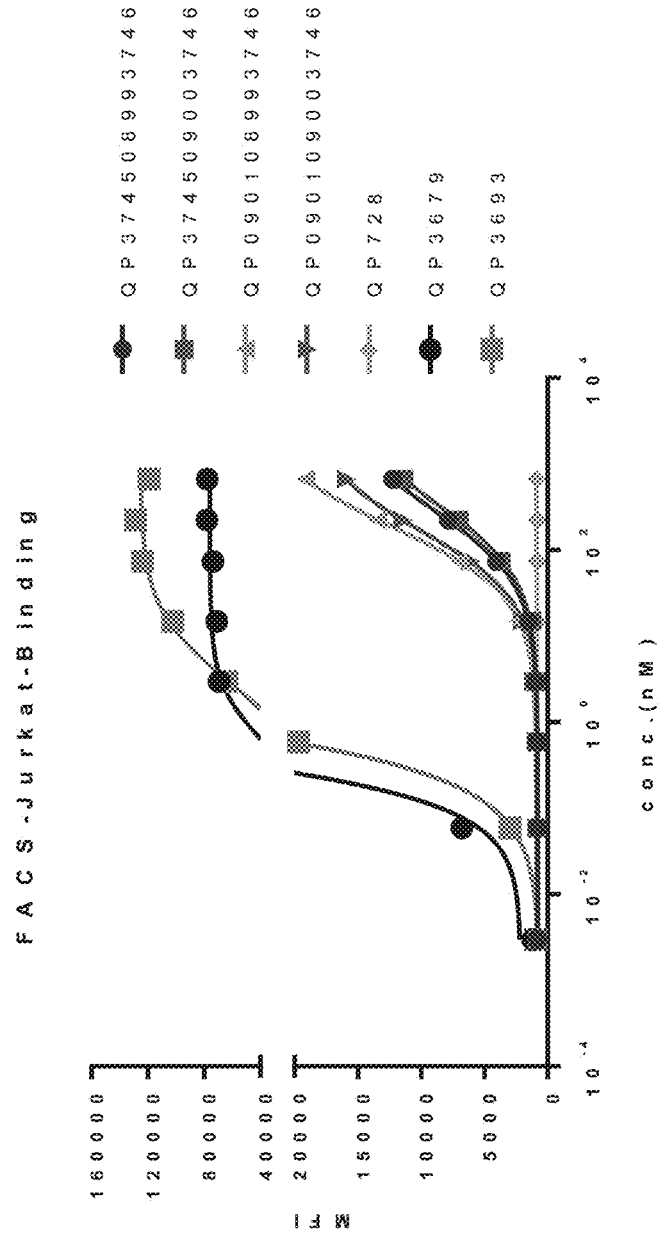


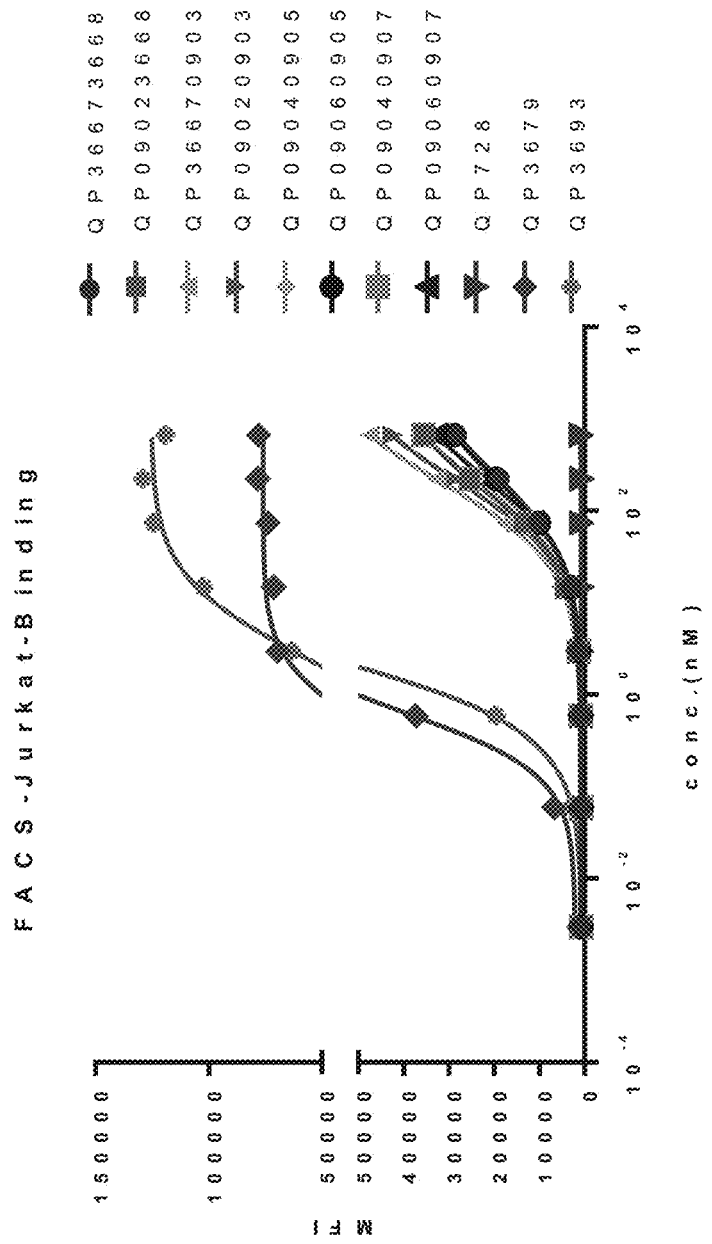
FIG. 30

QP36673668	32.39
QP09023668	18.5
QP36670903	26.63
QP09020903	24.81
QP09040905	6.539
QP09060905	7.832
QP09040907	7.387
QP09060907	8.511
QP728	36.65
QP33123313	1640
QP14611463	3.81
QP3679	694.3
QP3693	121.8



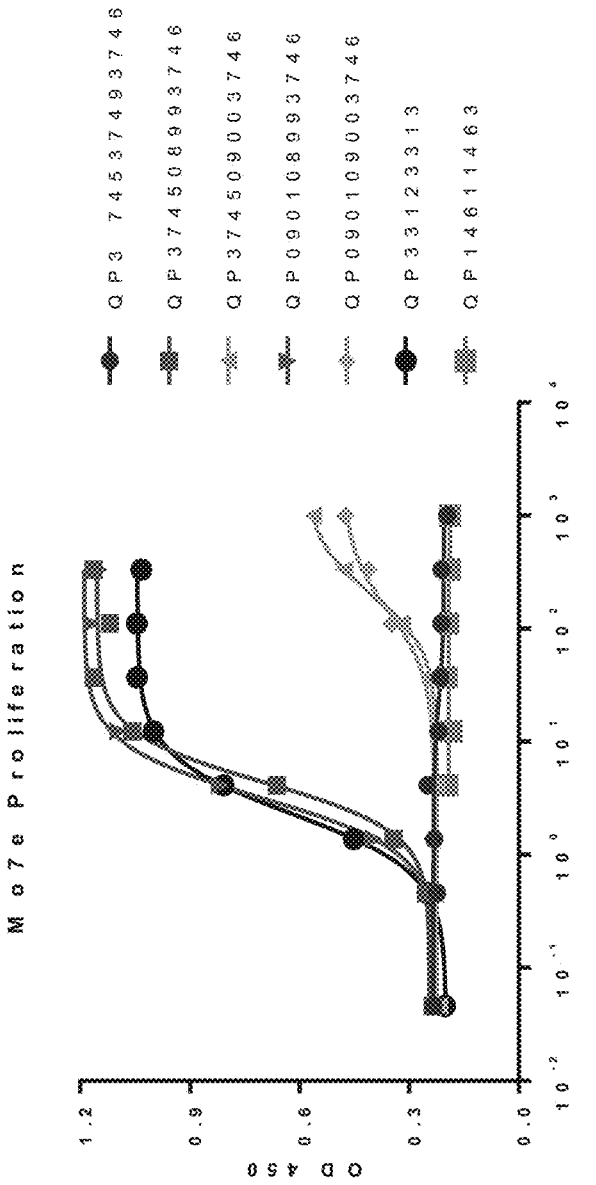
QP374508993746	282
QP374509003746	332.3
QP090108993746	186.1
QP090109003746	166.2
QP728	~ 1079
QP3679	0.6194
QP3693	3.034

FIG. 31



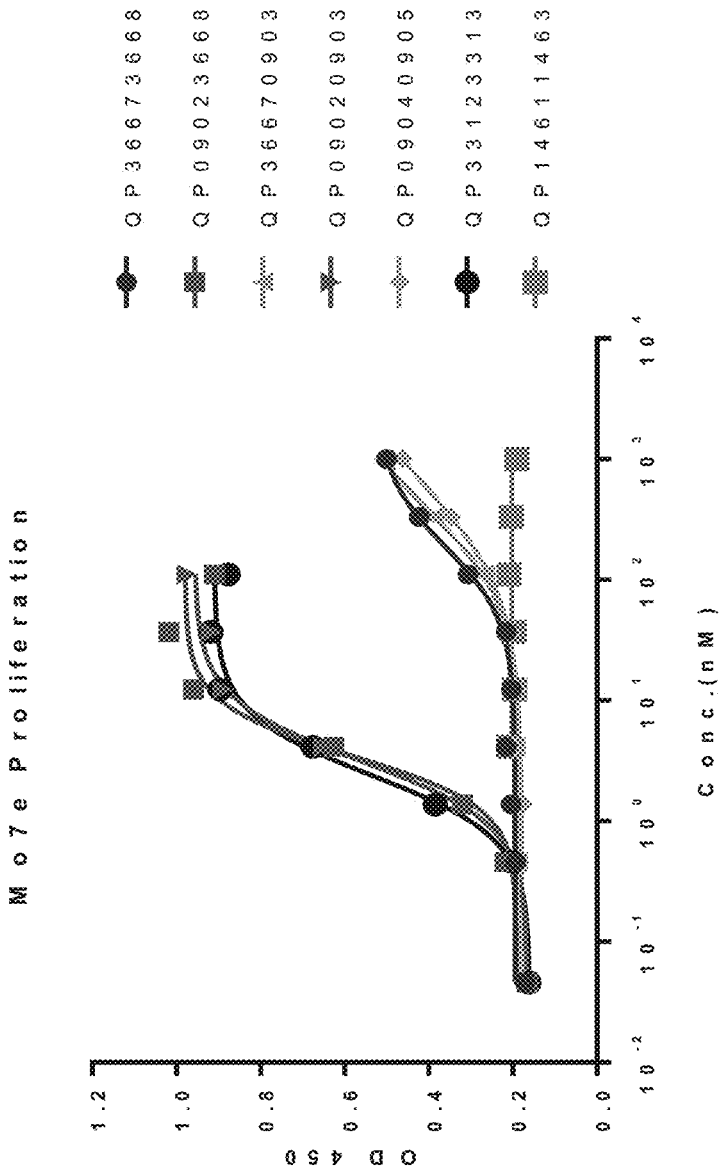
QP36673668	259.6
QP09023668	172.5
QP36670903	199.9
QP09020903	211.8
QP09040905	255.4
QP09060905	213
QP09040907	178.8
QP09060907	234.7
QP728	~ 1079
QP3679	0.6194
QP3693	3.034

FIG. 32



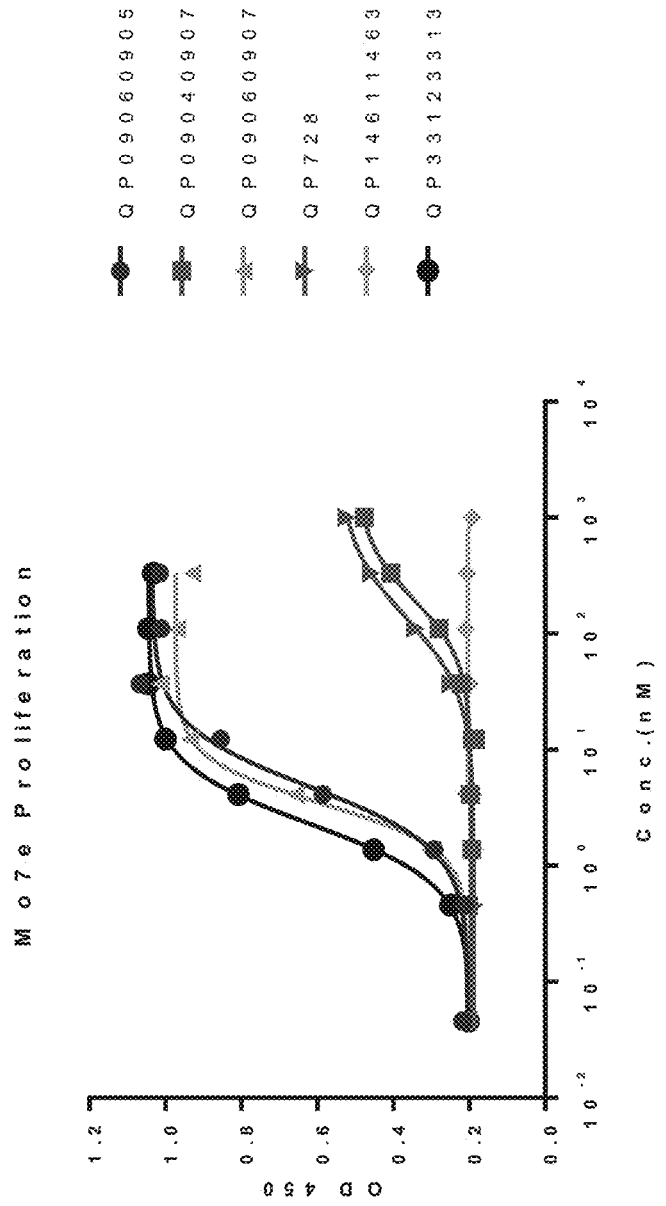
QP37450899746	4.391
QP37450900746	200.1
QP09010899746	3.207
QP09010900746	142.6
QP33123313	2.31

FIG. 33



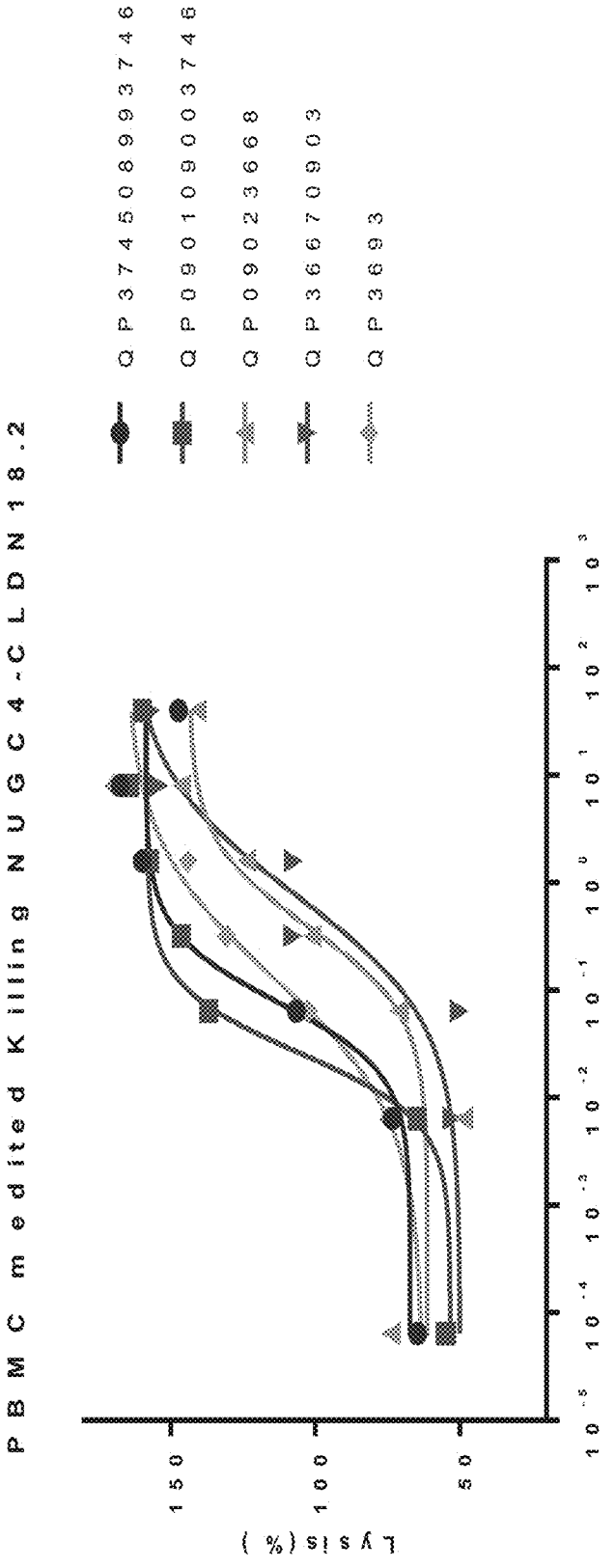
QP36673668	189.7
QP09023668	3.504
QP36670903	346.9
QP09020903	3.144
QP09040905	581.7
QP33123313	2.394
QP14611463	~ 2252

FIG. 34



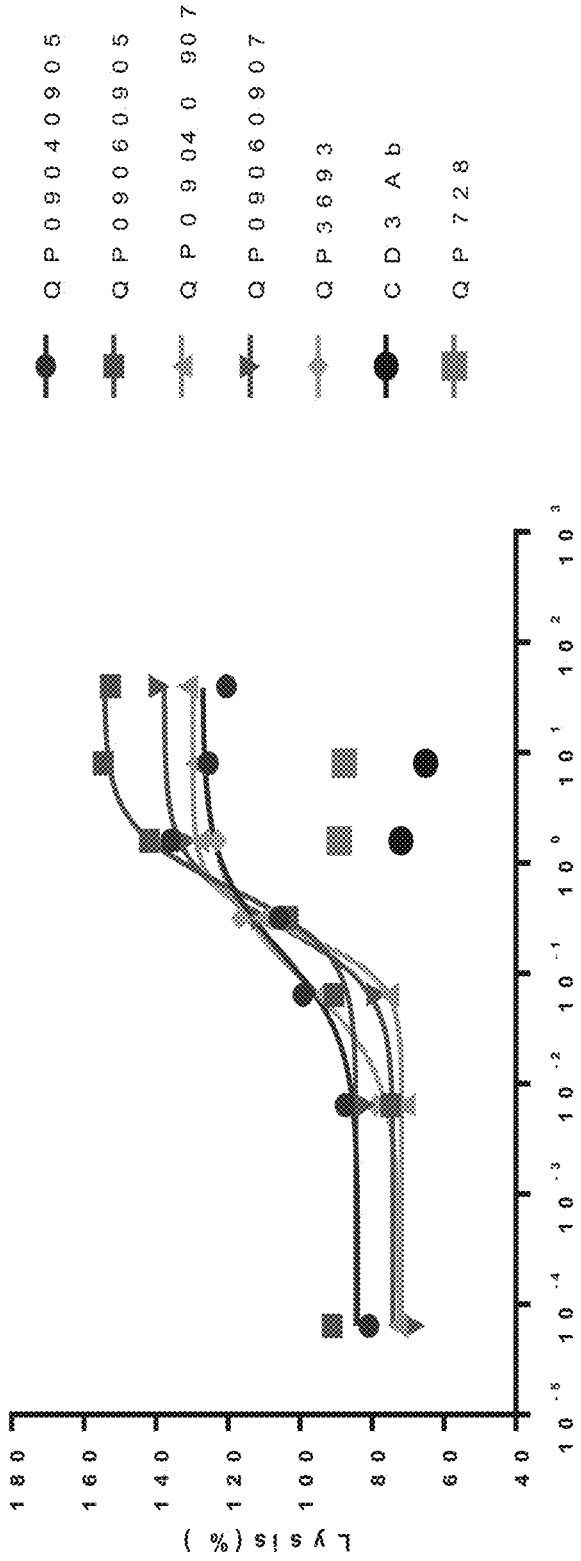
QP09060905	4.79
QP09040907	198.1
QP09060907	3.456
QP728	138.2
QP14611463	~ 2252
QP33123313	2.31

FIG. 35



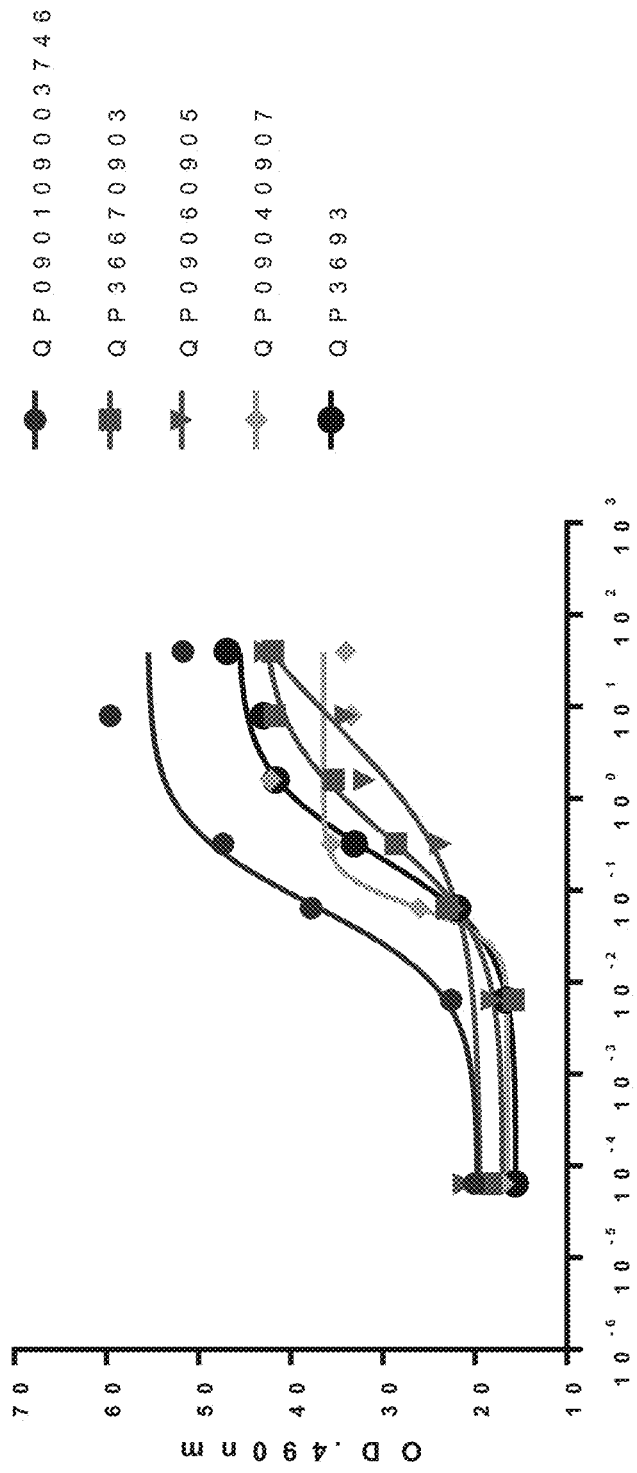
QP37450899374 6	0.07744
QP09010900374 6	0.02637
QP09023668	0.3896
QP36670903	0.7843
QP3693	0.1297

FIG. 36



QP09040905	0.1596
QP09060905	0.5942
QP09040907	0.23
QP09060907	0.2736
QP3693	0.09067
CD3 Ab	

FIG. 37



QP09010900 3746	0.06928
QP36670903	0.4341
QP09060905	6.386
QP09040907	0.06637
QP3693	0.241

FIG. 38

ANTI-CD3 ANTIBODY VARIANT, FUSION PROTEIN, AND APPLICATION

TECHNICAL FIELD

[0001] The present invention relates to the field of biomedicine technology, in particular to anti-CD3 antibody variant, fusion protein and application.

BACKGROUND

[0002] T lymphocytes, abbreviated as T cells, derived from bone marrow lymphoid stem cells after differentiation and maturation in the thymus, are distributed to immune organs and tissues throughout the body through lymph and blood circulation to exert immune functions. T cells are efficient killer cells that can quickly eliminate virus infected cells and cancer cells. The killing effect of T cells requires the formation of immune synapses, which is a process highly dependent on TCR recognizing the complex formed by MHC molecules on the surface of antigen presenting cells and the presented antigen peptides. The activated immune synapses act a killing effect by releasing cytotoxin and cytokine. In the process of formation of immune synapses, due to the limitation of the distance between T cells and target cells, bispecific or multi-specific antibody directed T cells need to simulate the formation of immune synapses, by bridging one end to T cell TCR receptors by targeting CD3, while bridging the other end to target cells by targeting target cell surface antigens. CD3 molecule is expressed on the surface of all mature T cells, and can non-covalently bind to TCR, forming a complete TCR-CD3 complex that participates in the immune response to antigenic stimulus. It is currently the most widely and successfully used trigger molecule on the surface of immune effector cells in bispecific antibodies. The bispecific antibody targeting CD3 can bind to CD3 on the surface of T cells and tumor cell surface antigens respectively, thereby narrowing the distance between cytotoxic T cells (Tc or CTL) and tumor cells, and directly activating T cells, inducing them to directly kill cancer cells, without relying on traditional T cell double activation signals.

[0003] Among the disclosed CD3 antibodies, OKT3 is a milestone antibody, which pioneered monoclonal antibody therapy for treating diseases as the first therapeutic antibody to be launched. SP34 is currently one of the few disclosed CD3 antibodies that can have species specific reactions with monkeys. In recent years, there are new scientific breakthroughs in the field of bispecific antibodies, leading to the development of various types of new CD3 bispecific antibodies (CD3-BsAbs). Currently, over 100 kinds of CD3-BsAbs of different structures have been successfully developed. The numerous forms of antibodies determine many characteristics thereof, such as half-life period, immunogenicity, type of therapeutic response, ability to penetrate solid tumors, and so on. Blinatumomab (CD19xCD3 in BiTE form) from Amgen had FDA approval in 2014 and is the most successful CD3-BsAb bispecific antibody by far. This drug is used to treat patients with recurrent or refractory acute lymphoblastic leukemia (ALL). Compared with standard chemotherapy, more than 40% of patients receiving Blinatumomab treatment can achieve complete or partial response (CR/PR), and the median overall survival can be improved by several months. In addition to Blinatumomab, there are currently many other CD3-BsAbs undergoing clinical trials, such as CD19, CD20, CD38, BCMA, CD33, and CD123. Furthermore, in a phase ½ clinical trial, patients with acute myeloid leukemia (AML) were treated with Flotetuzumab (CD123xCD3-BsAb) from MacroGenics with an overall response rate (ORR) of 30%. In another phase ½ clinical trial of Epcoritamab (CD20xCD3-BsAb) from Abbvie/Gemab company, 44% of patients with diffuse lymphoid large B-cell tumor (DLBCL) showed complete response (CR) and 11% of that showed partial response (PR), while patients with follicular lymphoma had 100% response (PR). Many other CD20xCD3 bispecific antibodies have also achieved similar outstanding results. For example, in NSG mice, REGN1979 (CD20xCD3-BsAb) from Regeneron could have a better control over tumor growth than Rituximab (CD20 monoclonal antibody) from Roche, which further proved the efficacy of CD3 bispecific antibodies. The latest data on the CD20xCD3 T cell binding bispecific antibody Glofitamab (formerly known as CD20-TCB) from Roche treating the recurrent or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) patients has been collected. This extended study involved DLBCL patients who were overtreated and highly refractory, with 58.3% of patients having no response to their initial treatment, and about one-third (33.1%) patients having received CAR-T cell therapy formerly. According to the Independent Review Committee (IRC) evaluation, at a median follow-up of 12.6 months, 39.4% of patients (61/155) achieved CR (the primary efficacy endpoint), and half of patients (51.6%; 80/155) achieved overall remission (the proportion of patients with partial response [PR]+complete response [CR]; the secondary efficacy endpoint). In terms of safety, cytokine release syndrome (CRS) was the most common adverse event, occurred in 63.0% of patients. CRS events are predictable, typically occur at a low level (mainly level 1 [47.4%] or level 2 [11.7%]) and occur at the initial dose, with only one patient discontinuing Glofitamab treatment due to CRS. The incidence of CRS at level 3 and above is relatively low (3.9%), and there are no level 5 events. Glofitamab has a novel "2:1" structural pattern, comprising two Fab regions targeting CD20 and one Fab region targeting CD3.

[0004] Amgen's Blinatumomab has shown in clinical trials that cytokine storm (CRS) is one of its most important toxic side effects. Tumor cells expressing CD19, when in the same environment as a large number of healthy B and T cells, may cause sudden CD3-BsAb mediated T cells activation, resulting in excessive release of inflammatory cytokines such as IFN-γ, IL-6 and TNF-α and so on, ultimately leading to symptoms from fever to multiple organ dysfunction. However, CRS is not a unique toxic side effect of Blinatumomab. In fact, CRS is frequently present in most CD3-BsAbs and CAR-T treatments. A humanized mouse model has shown that the main mediator of CD3-BsAb induced CRS is TNF-α produced by activated T cells, which leads to a large number of inflammatory cytokines secreted by monocytes. It has been found that CRS can be effectively alleviated by blocking upstream TNF-α and its downstream IL-1β or IL-6. In addition, several preclinical studies conducted in mouse and monkey models have shown that reducing the affinity of CD3 (i.e., using "weaker" CD3) can also reduce the level of cytokine storm.

[0005] Interleukin-15 (IL-15) is a 14-15 kDa cytokine that is crucial for the function of NK cells, NKT cells, and memory CD8+T cells. IL-15 binds to its receptor IL-15Ra to

produce a complex with extremely high biological potency, IL-15 super agonist (IL-15 SA), which is then transduced and transported to target cells together. IL-15 SA strongly activates cells that express IL-15R, especially NK cells/T cells, thereby promoting anti-tumor and antiviral functions. IL-15 has a wide range of immune regulatory effects and can participate in regulating the survival, proliferation, and function of T cells, especially NK cells and memory CD8+T cells. IL-15 and IL-2 have very similar structures and belong to the spiral cytokine family. The heterotrimer receptor of IL-15 shares IL-2R/IL-15 RB (CD122) and the same γc chain (CD 132) with IL-2 receptor. Due to these common receptor components and the shared JAK 1/JAK 3/STAT 5 signaling pathway, IL-15 and IL-2 have the same functions comprising stimulating T cell proliferation, producing cytotoxic T lymphocytes, stimulating B cell to produce immunoglobulins, and producing and sustaining NK cells. In many adaptive immune responses, IL-2 and IL-15 have unique and often competitive roles. There are four main roles: 1. IL-2 can regulate the activation of Tregs cells, while IL-15 cannot. 2. IL-2 can inhibit T cell response by activating induced death of CD8+ effector T cells. 3. IL-15 plays an essential role in the differentiation of NK, CD8+ effector cells, and memory phenotype CD8+ T cells. 4. Preclinical studies have shown that the toxicity of IL-15 is different from that of IL-2, and IL-15 shows almost no vascular capillary leakage compared to IL-2. These factors make IL-15 a more promising cytokine in tumor immune strategies. At present, several IL-15 targeted products are still in clinical trials, with the most noteworthy being the IL-15 super agonist N-803, a fusion protein co-expressed by IL-15 protein N72D mutation combined with IL-15Ra and IgG1Fc. On May 23, 2022, ImmunityBio submitted the marketing application of IL-15 super agonist N-803 to FDA for combined treatment with Bacille Calmette-Guerin (BCG) for non-muscle invasive bladder cancer (NMIBC) that does not respond to BCG. The clinical data released in 2021 showed that the combined treatment of N-803+BCG had a significant effect, with a CR rate of 71% (59/83) and an average CR maintenance time of 24.1 months. A phase 1 clinical trial showed that the combined treatment of Nivolumab (PD-1 antibody, Opdivo) and N-803 for metastatic non-small cell lung cancer can significantly prolong the long-term survival of patients. Genentech collaborates with Xencor to develop IL-15 cytokine XmAb®24306, and a clinical study is currently carried out for combined treatment of XmAb®24306 and Tecentriq. SHR-1501 (IL-15 fusion protein) from Hengrui Pharmaceuticals was approved for clinical trials on May 14, 2019. Moreover, SHR-1316 (PD-L1 monoclonal antibody) will be used in combination with SHR-1501 for the treatment of advanced malignant tumor patients who have failed treatment.

[0006] At present, there is still in need of developing CD3 bispecific antibodies for treatment, and how to solve the challenges faced in solid tumors and improve the safety of CD3-BsAb bispecific antibodies require further research and development.

DISCLOSURE OF THE INVENTION

[0007] The first purpose of the present invention is to provide an anti-CD3 antibody variant, which comprises a heavy chain variable region and a light chain variable region; the heavy chain variable region comprises: VHCDR1, VHCDR2, and VHCDR3; the light chain variable region comprises: VLCDR1, VLCDR2, and VLCDR3; the amino acid sequences of the anti-CD3 antibody comprises VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 shown in SEQ ID NO: 29-34; the mutation site of the anti-CD3 antibody variant comprises any one or more sites selected from the following group: position 10 of SEQ ID NO: 30, positions 2 and 7 of SEQ ID NO: 31, positions 3 and 4 of SEQ ID NO: 33, and positions 4, 5, 6, and 7 of SEQ ID NO: 34.

[0008] Preferably, the mutation is the substitution of amino acids.

[0009] Preferably, the mutation site of the variant comprises any one or more sites selected from the following group: A in position 10 substituted with E in SEQ ID NO: 30; G in position 2 substituted with S, and S in position 7 substituted with G in SEQ ID NO: 31; N in position 3 substituted with W, and K in position 4 substituted with L in SEQ ID NO: 33; Y in position 4 substituted with N or R, S in position 5 substituted with K, N in position 6 substituted with G, and L in position 7 substituted with G in SEQ ID NO: 34.

[0010] Preferably, the amino acid sequence of VHCDR2 is shown in SEQ ID NO: 35; alternatively, the amino acid sequence of VHCDR3 is shown in SEQ ID NO: 36; alternatively, the amino acid sequence of VLCDR2 is shown in SEQ ID NO: 37 or 38; alternatively, the amino acid sequence of VLCDR3 is shown in SEQ ID NO: 39, 40, or 41.

[0011] Preferably, the amino acid sequences of VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 are shown in any one of the following groups:

[0012] (1) SEQ ID NOs: 29, 35, 31, 32, 37, 39;

[0013] (2) SEQ ID NOs: 29, 35, 36, 32, 37, 40;

[0014] (3) SEQ ID NOs: 29, 35, 36, 32, 38, 41.

[0015] Preferably, the heavy chain variable region and/or light chain variable region of the antibody variant are selected from the heavy chain variable region and/or light chain variable region of the sequence as shown in or have at least 90% sequence identity with SEQ ID NO: 1, 2, or 3.

[0016] Preferably, there is a mutation used to form a disulfide bond between the heavy chain variable region and the light chain variable region, and the mutation site comprises any one or more of the following combination forms. The mutation site is EU numbering, and the heavy chain variable region is represented by VH, and the light chain variable region is represented by VL:

	Disulfide bond mutation site	
	VH	VL
Combination 1	37C	95C
Combination 2	44C	100C
Combination 3	44C	105C
Combination 4	45C	87C
Combination 5	100C	50C
Combination 6	100bC	49C
Combination 7	98C	46C
Combination 8	101C	46C
Combination 9	105C	43C
Combination 10	106C	57C

[0017] Preferably, the anti-CD3 antibody variant further comprises: a heavy chain constant region selected from human IgG1, IgG2, IgG3, or IgG4 or a variant thereof; and the light chain constant region selected from human κ, λ or

a variant thereof; wherein the heavy chain constant region comprises: an Fc fragment or a variant thereof.

[0018] Preferably, the antibody variant is an scFv, which comprises a heavy chain variable region, a light chain variable region, and a linker connecting the heavy chain variable region and the light chain variable region. The amino acid sequence of the linker is preferably several GGGGS replicates, more preferably three GGGGS replicates.

[0019] Another purpose of the present invention is to provide the application of the anti-CD3 antibody variant in the preparation of drugs for inhibiting or treating cancer.

[0020] Preferably, the cancer is selected from the following cancers or occurs in the following areas: colorectal, breast, ovary, pancreas, stomach, prostate, kidney, cervix, bone marrow cancer, lymphatic cancer, leukemia, thyroid, endometrium, uterus, bladder, neuroendocrine, head and neck, liver, nasopharyngeal, testicle, small cell lung cancer, non-small cell lung cancer, melanoma, basal cell skin cancer, squamous cell skin cancer, dermatofibrosarcoma protuberans, Merkel cell carcinoma, glioblastoma, glioma, sarcoma, mesothelioma, and myelodysplastic syndrome.

[0021] Another purpose of the present invention is to provide a nucleic acid molecule that encodes the anti-CD3 antibody variant.

[0022] Another purpose of the present invention is to provide an expression vector comprising the aforementioned nucleic acid molecule.

[0023] Another purpose of the present invention is to provide a protein molecule against tumor associated antigen (TAA)/CD3, which is in a form of heterodimer, and comprises a first monomer and a second monomer;

[0024] The first monomer comprises: (a) an Fd fragment; (b) a light chain fragment and a first Fc chain; the second monomer comprises: (a) an Fd fragment; (b) a light chain fragment, an anti-CD3 antibody fragment, and a second Fc chain; the light chain fragment comprises a VL domain and a CL domain; the Fd fragment comprises a VH domain and a CH1 domain; in the first monomer or the second monomer, the light chain fragment pairs with the Fd fragment to form an anti-TAA Fab domain; wherein the light chain fragment of the first monomer is fused with the first Fc chain; the N-terminus of the anti-CD3 antibody fragment is fused with the light chain fragment of the second monomer, and the C-terminus is fused with the second Fc chain;

[0025] Alternatively, the first monomer comprises: (a) an Fd fragment; (b) a light chain fragment, a cytokine functional region, and a first Fc chain; the second monomer comprises: (a) an Fd fragment; (b) a light chain fragment, an anti-CD3 antibody fragment, and a second Fc chain; the cytokine functional region comprises IL-15 and IL-15Ra; wherein the N-terminus of the cytokine functional region is fused with the light chain fragment of the first monomer, and the C-terminus is fused with the first Fc chain; the N-terminus of the anti-CD3 antibody fragment is fused with the light chain fragment of the second monomer, and the C-terminus is fused with the second Fc chain;

[0026] Alternatively, the first monomer comprises: an anti-TAA antibody fragment, a cytokine functional region, and a first Fc chain; the second monomer comprises: an anti-TAA antibody fragment, an anti-CD3 antibody fragment, and a second Fc chain; wherein the N-terminus of the cytokine functional region is fused with the anti-TAA antibody fragment of the first monomer, and the C-terminus is fused with the first Fc chain; The N-terminus of the anti-CD3 antibody fragment is fused with the anti-TAA antibody fragment of the second monomer, and the C-terminus is fused with the second Fc chain;

[0027] The first Fc chain and the second Fc chain are interchangeable.

[0028] Preferably, the anti-TAA antibody fragment is in the form of scFv, comprising: a heavy chain variable region (VH), a light chain variable region (VL), and a linker connecting the heavy chain variable region and the light chain variable region; from the N-terminus to the C-terminus of the peptide chain, the fusion order of amino acids of the anti-TAA antibody fragment is "VH~VL", or "VL~VH"; wherein, "~" represents a linker; alternatively, the anti-CD3 antibody fragment is in the form of scFv, comprising: a heavy chain variable region (VH), a light chain variable region (VL), and a linker connecting the heavy chain variable region and the light chain variable region; from the N-terminus to the C-terminus of the peptide chain, the fusion order of the amino acids of the anti-CD3 antibody fragment is "VH~VL", or "VL~VH"; wherein, "~" represents a linker; alternatively, from the N-terminus to the C-terminus of the peptide chain, the fusion order of the amino acid fragments of the cytokine functional region is "IL-15~IL-15Ra", or "IL-15Ra~IL-15"; wherein, "~" represents a linker; preferably, the sequence of IL-15~IL-15Ra is shown in SEQ ID NO: 42, and the sequence of IL-15Ra~IL-15 is shown in SEQ ID NO: 43.

[0029] Preferably, the amino acid sequence of the anti-CD3 antibody fragment is selected from an antibody, an antibody fragment, a single domain antibody, or a humanized form thereof that specifically binds to CD3; preferably, the amino acid sequence of the anti-CD3 antibody fragment is selected from SP34, OKT3, UCTH1 or a derivative thereof.

[0030] Preferably, the anti-CD3 antibody fragment comprises a heavy chain variable region and a light chain variable region; the heavy chain variable region of the anti-CD3 antibody fragment comprises: VHCDR1, VHCDR2, and VHCDR3; the light chain variable region of the anti-CD3 antibody fragment comprises: VLCDR1, VLCDR2, VLCDR3; the amino acid sequences of VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 are shown in any set of sequences of the anti-CD3 antibody variant according to claim **5**.

[0031] Preferably, IL-15Ra and IL-15 form an IL-15/IL-15Ra complex; IL-15 comprises: IL-15 and mutations, truncations, and various derivatives thereof that can bind to IL-15Ra; IL-15Ra comprises: IL-15Ra and mutations, truncations, and various derivatives thereof that can bind to IL-15; preferably, the IL-15/IL-15Ra complex includes but is not limited to any one of the mutation modes shown in the following combinations, and the numbering method is to start counting from the first amino acid in the amino acid sequence of IL-15 or IL-15Ra as the first position; preferably, the maternal sequence of IL-15 is shown in SEQ ID NO: 44; the maternal sequence of the IL-15Ra is shown in SEQ ID NO: 45:

Combination	IL15	IL5Ra
1	wt	D96
2	wt	D96/P97

-continued

Combination	IL15	IL5Ra
3	wt	D96/P97/A98
4	E87C	D96/C97
5	E87C	D96/P97/C98
6	E87C	D96/C97/A98
7	V49C	S40C
8	L52C	S40C
9	E89C	K34C
10	Q48C	G38C
11	E53C	L42C
12	C42S	A37C
13	L45C	G38C
14	L45C	A37C

[0032] Preferably, the IL-15 includes but is not limited to any one of the mutation modes shown in the following combinations, and the numbering method is to start counting from the first amino acid in the amino acid sequence of IL-15 as the first position; preferably, the maternal sequence of IL-15 is shown in SEQ ID NO: 44:

Combination	IL15 mutation
1	N1D
2	N4D
3	D8N
4	D30N
5	D61N
6	E64Q
7	N65D
8	Q108E

-continued

Combination	IL15 mutation
9	N1D/D61N
10	N1D/E64Q
11	N4D/D61N
12	N4D/E64Q
13	D8N/D61N
14	D8N/E64Q
15	D61N/E64Q
16	E64Q/Q108E
17	N1D/N4D/D8N
18	D61N/E64Q/N65D
19	N1D/D61N/E64Q/Q108E
20	N4D/D61N/E64Q/Q108E

[0033] Preferably, the TAA is selected from: CD20, CD19, CD30, CD33, CD38, CD40, CD52, slamf7, GD2, CD24, CD47, CD133, CD239, CD276, PD-1, CEA, Epcam, Trop2, TAG72, MUC1, MUC16, mesothelin, folr1, CLDN18.2, PDL1, EGFR, EGFR VIII, C-MET, HER2, FGFR2, FGFR3, PSMA, PSCA, EphA2, ADAM17, 17-A1, NKG2D ligands, MCSP, LGR5, SSEA3, SLC34A2, BCMA, GPNMB or Glypican-3.

[0034] Preferably, the first Fc chain and the second Fc chain are polymerized to form an Fc fragment; the Fc fragment is selected from human IgG1 Fc, human IgG2 Fc, human IgG3 Fc, human IgG4 Fc or a variant thereof, preferably from IgG1 Fc, or human IgG4 Fc or a variant thereof; the protein molecule is in a form of Fc heterodimer; preferably, the Fc heterodimer includes but is not limited to a combination of the following mutations, according to EU numbering:

Combination	FC	Heterodimer mutation (EU numbering)
1	first FC chain	T366Y
	second FC chain	Y407T
2	first FC chain	T366W
	second FC chain	T366S/L368A/Y407V
3	first FC chain	S354C/T366W
	second FC chain	Y349C/T366S/L368A/Y407V
4	first FC chain	S364H/F405A
	second FC chain	Y349T/T394F
5	first FC chain	T350V/L351Y/F405A/Y407V
	second FC chain	T350V/T366L/K392L/T394W
6	first FC chain	K392D/K409D
	second FC chain	E356K/D399K
7	first FC chain	D221EP228E/L368E
	second FC chain	D221R/P228R/K409R
8	first FC chain	K360EK409W
	second FC chain	Q347R/D399V/F405T
9	first FC chain	K360E/K409W/Y349C
	second FC chain	Q347R/D399V/F405T/S354C
10	first FC chain	K370E/K409W
	second FC chain	E357ND399VF405T
11	first FC chain	F405L
	second FC chain	K409R

-continued

Combination	FC	Heterodimer mutation (EU numbering)
12	first FC chain	K360D/D399M/Y407A
	second FC chain	E345R/Q347R/T366V/K409V
13	first FC chain	Y349S/K370Y/T366M/K409V
	second FC chain	E356G/E357D/S364Q/Y407A
14	first FC chain	L351D/L368E
	second FC chain	L351K/T366K
15	first FC chain	GQPFRPEVHLIPPSREMTKNQV SLTCLARGFYPKDAVEWESNGQ PENNYKTTPSRQEPSQGTTTFA VTSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKTEL
	second FC chain	GQPREPQVYTPPPSEEAINELV ILTCLVKGFYPSDAVEWLQGSQ ELPREKYLTWAPVLDSDGSFFL YSLRVAAEDWKKGDTFSCSVM HEALHNHYTQKSDR
16	first FC chain	L368D/K370S
	second FC chain	E357Q/S364K
17	first FC chain	S354C/T366W/K409A
	second FC chain	Y349C/T366S/L368A/ Y407V/F405K
18	first FC chain	S354C/T366W/F405K/ K360E/Q347E
	second FC chain	Y349C/T366S/L368A/ Y407V/Q347R/T394W
19	first FC chain	T366W/K409A
	second FC chain	T366S/L368G/Y407A/F405K
20	first FC chain	knobs (T366W/F405K)
	second FC chain	holes (T366S/L368G/Y407A/K409A)
21	first FC chain	Q347A/S364K/T366VK370T/K392 YF405S/Y407V/K409W/T411N
	second FC chain	Q347E/Y349AL351F/S364T/T366 V//K370T/T394D/V397L/D399E/ D401Q/F405A/Y407S/K409R/ T411R
22	first FC chain	K274Q/N276K/Y300F/A339T/Q34 7A/S364K/T366V/K370T/N384S /K392Y/V397M/F405S/Y407V/K4 09W/T411N/V422I/H435R/Y436F
	second FC chain	Q347E/Y349A/L351F/S364T/T366 V/K370T/T394D/V397L/D399E/ D401Q/F405A/Y407S/K409R/T411 R

[0035] Preferably, the protein molecule comprises an Fc fragment that selectively eliminates immune effector functions, including but not limited to a combination of the following mutations, according to EU numbering:

IgG	FC Mutate(EU numbing)
IgG1	L234A, L235A
	L234A, L235A, P329G
	L234F, L235E, P331S
	D265A, N297A
	L234F, L235E, N297A
	L234F, L235E, D265A
	L234A, L235E, P331S

-continued

IgG	FC Mutate(EU numbing)
	L234A, L235E, N297A
	L234A, L235E, D265A
	L234A, L235A, P331S
	L234A, L235A, N297A
	L234A, L235A, D265A
	L235E, D265A, P331S
	L235E, N297A, P331S
	L235E, N297A
	L235A, D265A, P331S
	L235A, N297A, P331S
	N297Q
	N297A

-continued

IgG	FC Mutate(EU numbing)
	N297G
	A287C, N297G, L306C
	R292C, N297G, V302C
hIgG4	S228P, L235E, P329G
	S228P, L235E
	S228P, F234A, L235E
	S228P, F234A, L235A
IgG2m4	ASTKGPSVFPLAPCSRSTSE
	STAALGCLVKDYFPEPVTVS
	WNSGALTSGVHTFPAVLQSS
	GLYSLSSVVTVPSSNFGTQT
	YTCNVDHKPSNTKVDKTVER
	KCCVECPPCPAPPVAGPSVF
	LFPPKPKDTLMISRTPEVTC
	VVVDVSQEDPEVQFNWYVDG
	VEVHNAKTKPREEQFNSTYR
	VVSVLTVLHQDWLNGKEYKC
	KVSNKGLPSSIEKTISKAKG
	QPREPQVYTLPPSQEEMTKN
	QVSLTCLVKGFYPSDIAVEW
	ESNGQPENNYKTTPPVLDSD
	GSFFLYSRLTVDKSRWQEGN
	VFSCSVMHEALHNHYTQKSL
	SLSLGK
	N297A
	N297Q
	N297G

[0036] Preferably, the anti-tumor associated antigen (TAA)/anti-CD3 protein molecule is obtained by fusing amino acid fragments shown in any one of the following groups of sequences:

[0037] (1) SEQ ID NO:05, SEQ ID NO:06, SEQ ID NO:07;

[0038] (2) SEQ ID NO:08, SEQ ID NO:06, SEQ ID NO:07;

[0039] (3) SEQ ID NO:09, SEQ ID NO:06, SEQ ID NO:07;

[0040] (4) SEQ ID NO:10, SEQ ID NO:06, SEQ ID NO:07;

[0041] (5) SEQ ID NO:05, SEQ ID NO:17, SEQ ID NO:07;

[0042] (6) SEQ ID NO:01, SEQ ID NO:18, SEQ ID NO:07;

[0043] (7) SEQ ID NO: 19, SEQ ID NO: 17, SEQ ID NO:07;

[0044] (8) SEQ ID NO:19, SEQ ID NO:18, SEQ ID NO:07;

[0045] (9) SEQ ID NO:20, SEQ ID NO:21;

[0046] (10) SEQ ID NO:22, SEQ ID NO:21;

[0047] (11) SEQ ID NO:20, SEQ ID NO:23;

[0048] (12) SEQ ID NO:22, SEQ ID NO:23;

[0049] (13) SEQ ID NO:24, SEQ ID NO:25;

[0050] (14) SEQ ID NO:26, SEQ ID NO:25;

[0051] (15) SEQ ID NO:24, SEQ ID NO:27;

[0052] (16) SEQ ID NO:26, SEQ ID NO:27.

[0053] Another purpose of the present invention is to provide a nucleic acid molecule that encodes the anti-tumor associated antigen (TAA)/anti-CD3 protein molecule.

[0054] Another purpose of the present invention is to provide an application of the anti-tumor associated antigen (TAA)/anti-CD3 protein molecule in the preparation of drugs for inhibiting or treating cancer, wherein the cancer is selected from the following cancers or occurs in the following areas: colorectal, breast, ovary, pancreas, stomach, prostate, kidney, cervix, bone marrow cancer, lymphatic cancer, leukemia, thyroid, endometrium, uterus, bladder, neuroendocrine, head and neck, liver, nasopharyngeal, testicle, small cell lung cancer, non-small cell lung cancer, melanoma, basal cell skin cancer, squamous cell skin cancer, dermatofibrosarcoma protuberans, Merkel cell carcinoma, glioblastoma, glioma, sarcoma, mesothelioma, and myelodysplastic syndrome.

[0055] Another purpose of the present invention is to provide an anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein, comprising two polypeptides, any one of which comprises: an anti-TAA antibody fragment, a cytokine functional region, and an Fc fragment; the anti-TAA antibody fragment is in the form of scFv; the cytokine functional region comprises IL-15 and IL-15Ra; the N-terminus of the cytokine functional region is fused with the anti-TAA antibody fragment, and the C-terminus is fused with the Fc fragment.

[0056] Preferably, in the anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein, the IL-15Ra and IL-15 form an IL-15/IL-15Ra complex; the IL-15 comprises: IL-15 and mutations, truncations, and various derivatives thereof that can bind to IL-15Ra; the IL-15Ra comprises: IL-15Ra and mutations, truncations, and various derivatives thereof that can bind to IL-15; preferably, the IL-15/IL-15Ra complex includes but is not limited to any one of the mutation modes shown in the following combinations, wherein the numbering method is to start counting from the first amino acid in the amino acid sequence of IL-15 or IL-15Ra as the first position; preferably, the maternal sequence of IL-15 is shown in SEQ ID NO: 44; the maternal sequence of IL-15Ra is shown in SEQ ID NO: 45:

Combination	IL15	IL15Ra
1	wt	D96
2	wt	D96/P97
3	wt	D96/P97/A98
4	E87C	D96/C97
5	E87C	D96/P97/C98
6	E87C	D96/C97/A98
7	V49C	S40C
8	L52C	S40C
9	E89C	K34C
10	Q48C	G38C
11	E53C	L42C
12	C42S	A37C
13	L45C	G38C
14	L45C	A37C

[0057] Preferably, in the anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein, the IL-15 includes but is not limited to any one of the mutation modes shown in the following combinations, and the numbering method is to start counting from the first amino acid in the amino acid sequence of IL-15 as the first position; preferably, the maternal sequence of IL-15 is shown in SEQ ID NO: 44:

Combination	IL15 mutation
1	N1D
2	N4D

-continued

Combination	IL15 mutation
3	D8N
4	D30N
5	D61N
6	E64Q
7	N65D
8	Q108E
9	N1D/D61N
10	N1D/E64Q
11	N4D/D61N
12	N4D/E64Q
13	D8N/D61N
14	D8N/E64Q
15	D61N/E64Q
16	E64Q/Q108E
17	N1D/N4D/D8N
18	D61N/E64Q/N65D
19	N1D/D61N/E64Q/Q108E
20	N4D/D61N/E64Q/Q108E

[0058] Preferably, the anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein comprises an Fc fragment, which selectively eliminates immune effector functions, including but not limited to a combination of the following mutations, according to EU numbering:

IgG	FC Mutate(EU numbing)
IgG1	L234A, L235A
	L234A, L235A, P329G
	L234F, L235E, P331S
	D265A, N297A
	L234F, L235E, N297A
	L234F, L235E, D265A
	L234A, L235E, P331S
	L234A, L235E, N297A
	L234A, L235E, D265A
	L234A, L235A, P331S
	L234A, L235A, N297A
	L234A, L235A, D265A
	L235E, D265A, P331S
	L235E, N297A, P331S
	L235E, N297A
	L235A, D265A, P331S
	L235A, N297A, P331S
	N297Q
	N297A
	N297G
	A287C, N297G, L306C
	R292C, N297G, V302C
hIgG4	S228P, L235E, P329G
	S228P, L235E
	S228P, F234A, L235E
	S228P, F234A, L235A
IgG2m4	ASTKGPSVFPLAPCSRSTSE
	STAALGCLVKDYFPEPVTVS
	WNSGALTSGVHTFPAVLQSS
	GLYSLSSVVTVPSSNFGTQT
	YTCNVDHKPSNTKVDKTVER
	KCCVECPPCPAPPVAGPSVF
	LFPPKPKDTLMISRTPEVTC
	VVVDVSQEDPEVQFNWYVDG
	VEVHNAKTKPREEQFNSTYR
	VVSVLTVLHQDWLNGKEYKC
	KVSNKGLPSSIEKTISKAKG
	QPREPQVYTLPPSQEEMTKN
	QVSLTCLVKGFYPSDIAVEW
	ESNGQPENNYKTTPPVLDSD
	GSFFLYSRLTVDKSRWQEGN
	VFSCSVMHEALHNHYTQKSL

-continued

IgG	FC Mutate(EU numbing)
	SLSLGK
	N297A
	N297Q
	N297G

[0059] Preferably, any polypeptide chain of the anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein has an amino acid sequence shown in SEQ ID NO: 28, or has at least 90% sequence identity with it.

[0060] Another purpose of the present invention is to provide a nucleic acid molecule that encodes the anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein.

[0061] Another purpose of the present invention is to provide an application of the anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein in the preparation of drugs for inhibiting or treating cancer, wherein the cancer is selected from the following cancers or occurs in the following areas: colorectal, breast, ovary, pancreas, stomach, prostate, kidney, cervix, bone marrow cancer, lymphatic cancer, leukemia, thyroid, endometrium, uterus, bladder, neuroendocrine, head and neck, liver, nasopharyngeal, testicle, small cell lung cancer, non-small cell lung cancer, melanoma, basal cell skin cancer, squamous cell skin cancer, dermatofibrosarcoma protuberans, Merkel cell carcinoma, glioblastoma, glioma, sarcoma, mesothelioma, and myelodysplastic syndrome.

[0062] Compared to the prior art, the present invention has the following beneficial effects:

[0063] (1) The present invention mutates existing anti-CD3 antibody and obtains new anti-CD3 antibody variants.

[0064] (2) The present invention also provides antibody molecules with novel structures, which have good biological activity.

BRIEF DESCRIPTION OF THE DRAWINGS

[0065] FIG. **1** shows the binding of CD3 antibody SP34 and its mutants to Jurkat cells detected by FACS.

[0066] FIG. **2** shows the design diagram of the molecular format of bispecific antibody of anti-TAA (tumor associated antigen) and anti-CD3.

[0067] FIG. **3** shows the design diagram of the molecular format of QP372337241461.

[0068] FIG. **4** shows the design diagram of the molecular format of QP374437481461.

[0069] FIGS. **5** and **6** show the FACS detection results of CLDN18.2/CD3 bispecific antibody and other molecules binding to CLDN18.2.

[0070] FIGS. **7** and **8** show the FACS detection results of CLDN18.2/CD3 bispecific antibody and other molecules binding to CD3.

[0071] FIGS. **9** and **10** show the results of CLDN18.2/CD3 antibody and other molecules mediated PBMC killing human gastric cancer cells NUGC4 CLDN18.2.

[0072] FIG. **11** shows the results of CLDN18.2/CD3 antibody and other molecules mediated PBMC killing human lung cancer cells HCC827-CLDN18.2.

[0073] FIG. **12** shows the inhibitory curve of CLDN18.2/CD3 bispecific antibody molecule inhibiting tumor growth

in an in vivo animal model of CD3EGD HuGEMM mice subcutaneously transplanted colorectal cancer cell MC38-hCLDN18.2.

[0074] FIG. **13** shows the weight change curve of mice in each group after administration in an in vivo animal model of CD3EGD Hu GEMM mice subcutaneously transplanted colorectal cancer cell MC38-hCLDN18.2.

[0075] FIGS. **14** and **15** show the inhibitory curve of CLDN18.2/CD3 bispecific antibody molecule inhibiting tumor growth in a model of PBMC humanized NOG mice X-CLDN18.2/MIA PaCa-2 subcutaneously transplanted tumor.

[0076] FIGS. **16** to **19** show the structural design diagram of a type of multifunctional anti-TAA/CD3 and IL15/IL 15Ra-containing fusion protein.

[0077] FIGS. **20** to **27** show the structural design diagram of another type of multifunctional anti-TAA/CD3 and IL15/IL15Ra-containing protein.

[0078] FIG. **28** shows the structure design diagram of the TAA/IL15 bifunctional fusion protein activated by tumor targeting T cells/NK cells.

[0079] FIG. **29** shows the FACS detection results of CLDN18.2/CD3/IL 15 multifunctional fusion protein binding to CLDN18.2.

[0080] FIG. **30** shows the FACS detection results of CLDN18.2/CD3/IL15 and CLDN18.2/IL15 fusion protein binding to CLDN18.2.

[0081] FIG. **31** shows the FACS detection results of CLDN18.2/CD3/IL15 multifunctional fusion protein binding to CD3.

[0082] FIG. **32** shows the FACS detection results of CLDN18.2/CD3/IL15 and CLDN18.2/IL15 fusion protein binding to CD3.

[0083] FIGS. **33**, **34**, and **35** show the results of Mole cell proliferation experiment for detecting the activity of IL 15 multifunctional fusion protein.

[0084] FIGS. **36** and **37** show the results of CLDN18.2/CD3/IL15 mediated PBMC killing human gastric cancer cells NUGC4 CLDN18.2.

[0085] FIG. **38** shows the results of CLDN18.2/CD3/IL15 mediated PBMC killing human lung cancer cells HCC827-CLDN18.2.

BEST MODE OF THE INVENTION

[0086] The following is a further explanation of the technical solution of the present invention accompanying with drawings and embodiments.

[0087] The experimental methods without specific conditions in this experiment are usually in accordance with conventional conditions or conditions recommended by the manufacturer of raw materials or commodities. Reagents without specific sources are commercially available conventional reagents.

[0088] As used herein, "/" refers to "and". For example, anti-tumor associated antigen (TAA)/anti-CD3 bispecific antibody refer to antibody targeting both TAA and CD3 simultaneously.

[0089] The term "fusion" refers to connecting components directly by peptide bonds or using linker, or through intermolecular interactions. In a single peptide chain, fusion refers to the direct connection by peptide bonds or the use of linker. A "multifunctional fusion protein" refers to a protein that comprises two or more antigen-binding domains and can bind to two or more different epitopes (such as two, three, or more different epitopes). A multifunctional fusion protein may further comprise cytokines (such as IL-15, IL-15Ra), etc. The "fusion position" refers to the position of functional regions or structural domains in the peptide chain, indicating the connection order of each functional fragment on the peptide chain.

[0090] The term "polypeptide" refers to amino acid chain of any length, comprising protein and fragment thereof. The polypeptides are disclosed in amino acid residue sequences in the present invention. Those sequences are written from left to right in the direction from the amino end to the carboxyl end. According to the standard nomenclature, amino acid residue sequences are named by three-letter or single-letter codes, as follows: alanine (Ala, A), arginine (Arg, R), asparagine (Asn, N), aspartate (Asp, D), cysteine (Cys, C), glutathione (Gln, Q), glutamate (Glu, E), glycine (Gly, G), histidine (His, H), isoleucine (Ile, I), leucine (Leu, L), lysine (Lys, K), methionine (Met, M), phenylalanine (Phe, F), proline (Pro, P), serine (Ser, S), threonine (Thr, T), tryptophan (Trp, W), tyrosine (Tyr, Y), and valine (Val, V).

[0091] The term "single chain" refers to a molecule comprising amino acids linearly linked by peptide bonds.

[0092] The term "variant" or "mutant" refers to a polypeptide or polynucleotide that comprises different amino acids or nucleotides but maintains the basic characteristics. Generally, the differences between variants or between variant and maternal antibody are limited, and the amino acid sequences are very similar in general. In this description, the pre-mutated antibody or antibody fragment is referred to as maternal antibody, and the mutated antibody or antibody fragment is referred to as variant. The variant still has antigen-binding activity.

[0093] The term "antibody (Ab)" refers to an immunoglobulin molecule (Ig) that comprises at least one antigen-binding site and can specifically bind to antigen.

[0094] The term "antigen" refers to a substance that can induce an immune response in body and specifically bind to antibody. The binding of antibody to antigen relies on the interaction between the two, comprising hydrogen bonds, van der Waals forces, ionic bonds, and hydrophobic bonds. The region on the surface of an antigen to which an antibody binds is an "antigenic determinant" or "epitope". Generally, each antigen has multiple determinants.

[0095] The term "antibody" referred in the present invention should be understood in its broadest sense, and encompasses a monoclonal antibody (comprising full-length monoclonal antibody), polyclonal antibody, antibody fragment, and multi-specific antibody comprising at least two different antigen-binding domains (such as bispecific antibody). Antibody also comprises a murine antibody, a humanized antibody, a chimeric antibody, a human antibody, and an antibody from other origins. The antibody of the present invention can originate from any animal, including but not limited to, immunoglobulin molecules of human, non-human primate, mouse, rat, cow, horse, chicken, camel, alpaca, etc. Antibody can comprise additional alterations, such as non-natural amino acids, Fc effector functional mutations, and glycosylation site mutations. Antibody also comprises a post-translational modified antibody, a fusion protein comprising antigenic determinants of antibody, and immunoglobulin molecules comprising any other modification to the antigenic recognition sites, as long as these antibodies exhibit the desired biological activity. In other words, antibody comprises an immunoglobulin molecule

and an immune active fragment of immunoglobulin molecule, i.e. a molecule comprising at least one antigen-binding domain.

[0096] The basic structure of antibody is a Y-shaped monomer consisting of two identical heavy chains (H) and two identical light chains (L) connected by disulfide bonds. Each chain is composed of 2-5 domains (also known as functional regions) comprising approximately 110 amino acids, with similar sequences but different functions. The amino acid sequences have significant changes near the N-terminus of the light and heavy chains in antibody molecule, forming a structural domain called variable region (V region); the region with relatively constant amino acid sequence near the C-terminus is called the constant region (C region).

[0097] The V regions of the heavy and light chains are called VH and VL, respectively. There are three regions in VH and VL with highly variable composition and arrangement of amino acids, known as hypervariable region (HVR). These regions form a spatial conformation complementary to the antigen epitope, which is also known as the complementarity determining region (CDR). The three CDRs of VH are represented by VHCDR1, VHCDR2, and VHCDR3, while the three CDRs of VL are represented by VLCDR1, VLCDR2, and VLCDR3, respectively. A total of 6 CDRs from VH and VL form the antigen binding site. The diversity of amino acids in the CDR region is the molecular basis for the antibody to specifically bind to a large number of different antigens. The composition and arrangement of amino acids other than CDRs in the V region relatively have little change, which are called framework regions (FRs). VH and VL each have four framework regions, which are represented by FR1, FR2, FR3, and FR4, respectively. Each VH and VL is composed of three CDRs and four FRs, arranged from the amino-terminus to the carboxyl-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

[0098] According to the amino acid sequence of the heavy chain constant region of the antibody, human immunoglobulins can be divided into five classes: IgM, IgG, IgA, IgD, and IgE. It can be further divided into different subtypes (isotypes), for example, human IgG can be divided into IgG1, IgG2, IgG3, and IgG4; IgA can be divided into IgA1 and IgA2. No subtypes have been found for IgM, IgD, and IgE. According to the amino acid sequences of light chains, light chains can be divided as κ chain and λ chain. The antibodies of the present invention may be of any type (such as IgM, IgG, IgA, IgD, IgE) or subtype (such as IgG1, IgG2, IgG3, IgG4, IgA1, IgA2).

[0099] The constant regions of heavy and light chains are referred to as CH and CL, respectively. The heavy chain constant region of IgG, IgA, and IgD has three domains of CH1, CH2, and CH3, while the heavy chain constant region of IgM and IgE has four domains of CH1, CH2, CH3, and CH4.

[0100] The hinge region is located between CH1 and CH2 and is rich in proline, making it stretchable and bendy, which can change the distance between the Y-shaped arms and facilitate the simultaneous binding of both arms to antigen epitopes.

[0101] The term "Fab fragment" is a fragment of antigen binding (Fab), which refers to an antibody fragment comprising VL, VH, CL, and CH1 domains that binds to a single antigen epitope (monovalent). Those skilled in the field know that under certain conditions, certain parts of the antibody molecular chain are easily hydrolyzed into various fragments by proteolytic enzymes. Papain hydrolyzes an antibody molecule into two identical antigen-binding fragments (Fab) and one crystallizable fragment (Fc) from the near N-terminus of the hinge region.

[0102] The term "Fd fragment" refers to an antibody fragment consisting of VH and CH1 domains.

[0103] The terms "Fc", "Fc segment", "Fc fragment", and "Fc domain" refer to a crystallizable fragment, which has no antigen-binding activity and is the interaction site of antibody with effector molecule or cell surface Fc receptor (FcR). Fc fragments bind to cells with corresponding Fc receptors on their surface, resulting in different biological effects. In ADCC effect (antibody dependent cell mediated cytotoxicity), the Fab segment of the antibody binds to the antigen epitopes of virus infected cells or tumor cells, and its Fc segment binds to the FcR on the surface of killer cells (NK cells, macrophages, etc.) to mediate the direct killing of target cells by killer cells. The Fc fragment comprises constant region polypeptides of the antibody other than the heavy chain constant region CH1, i.e. the constant region domains CH2 and CH3 in the carboxyl end of the heavy chain constant region of human immunoglobulins IgA, IgD, and IgG, and three constant region domains CH2, CH3, and CH4 of the carboxyl end of the heavy chain constant region of human immunoglobulins IgE and IgM. The Fc fragment is usually selected from Human IgG1 Fc, Human IgG2 Fc, Human IgG3 Fc, Human IgG4 Fc or variants thereof, preferably from IgG1 Fc, or Human IgG4 Fc or variants thereof.

[0104] Fc may be composed of two chains. As used herein, the two chains of Fc fragment are described as the first Fc chain and the second Fc chain. The first Fc chain and the second Fc chain may be mutated separately, and is not particularly limited in the present invention. The Fc fragments may also refer to a single polypeptide chain in the Fc domain. The Fc segment of the antibody can selectively eliminate immune effector functions, including but not limited to the following combinations of mutations (according to EU numbering).

IgG	FC Mutate(EU numbing)
IgG1	L234A, L235A
	L234A, L235A, P329G
	L234F, L235E, P331S
	D265A, N297A
	L234F, L235E, N297A
	L234F, L235E, D265A
	L234A, L235E, P331S
	L234A, L235E, N297A
	L234A, L235E, D265A
	L234A, L235A, P331S
	L234A, L235A, N297A
	L234A, L235A, D265A
	L235E, D265A, P331S
	L235E, N297A, P331S
	L235E, N297A
	L235A, D265A, P331S
	L235A, N297A, P331S
	N297Q
	N297A
	N297G
	A287C, N297G, L306C
	R292C, N297G, V302C

-continued

IgG	FC Mutate(EU numbing)
hIgG4	S228P, L235E, P329G
	S228P, L235E
	S228P, F234A, L235E
	S228P, F234A, L235A
IgG2m4	ASTKGPSVFPLAPCSRSTSE
	STAALGCLVKDYFPEPVTVS
	WNSGALTSGVHTFPAVLQSS
	GLYSLSSVVTVPSSNFGTQT
	YTCNVDHKPSNTKVDKTVER
	KCCVECPPCPAPPVAGPSVF
	LFPPKPKDTLMISRTPEVTC
	VVVDVSQEDPEVQFNWYVDG
	VEVHNAKTKPREEQFNSTYR
	VVSVLTVLHQDWLNGKEYKC
	KVSNKGLPSSIEKTISKAKG
	QPREPQVYTLPPSQEEMTKN
	QVSLTCLVKGFYPSDIAVEW
	ESNGQPENNYKTTPPVLDSD
	GSFFLYSRLTVDKSRWQEGN
	VFSCSVMHEALHNHYTQKSL
	SLSLGK
	N297A
	N297Q
	N297G

[0105] The mutation designed Fc variants can form spatial filling effects, electrostatic steering, hydrogen bonding, hydrophobic interactions, etc. The interaction between Fc variants helps to form a stable heterodimer. The preferred mutation design is a "Knob in hole" mutation design.

[0106] ScFv (single chain antibody fragment), also known as single chain antibody, is formed by connecting the heavy chain variable region and light chain variable region of the antibody through a linker. The "linker" can also connect IL-15 to IL-15Ra, VH of CD3 antibody to VL of that, and ensure correct protein folding and peptide stability. The "linker" is preferably (GGGGS) n, wherein n can be 0, 1, 2, 3, 4, 5, or more. If the linker sequence is too short, it may affect the folding of the higher structure of the two proteins, thereby interfering with each other; if the linker peptide sequence is too long, it also involves immunogenicity issues, since the linker peptide sequence itself is a new antigen.

[0107] Tumor-associated antigen (TAA) refers to the antigen molecule present on tumor cells or normal cells, comprising embryonic protein, glycoprotein antigen, squamous cell antigen, etc., commonly used in clinical tumor diagnosis. Tumor-associated antigens are not exclusive to tumor cells, and can be synthesized in trace amounts by normal cells, but they are highly expressed during tumor cell proliferation, hence called "associated antigens". For example, tumor associated antigen can be CD20, CD19, CD30, CD33, CD38, CD40, CD52, slamf7, GD2, CD24, CD47, CD133, CD239, CD276, PD-1, CEA, Epcam, Trop2, TAG72, MUC1, MUC16, mesothelin, folr1, CLDN18.2, PDL1, EGFR, EGFR VIII, C-MET, HER2, FGFR2, FGFR3, PSMA, PSCA, EphA2, ADAM17, 17-A1, NKG2D ligands, MCSP, LGR5, SSEA3, SLC34A2, BCMA, GPNMB, or Glypican-3.

[0108] The term "vector" refers to a polynucleotide molecule that can transport another polynucleotide connected to it. One type of vector is a "plasmid", which is a circular double stranded DNA loop that can attach additional DNA segments. Another type of vector is a viral vector, where additional DNA segment can be integrated into the virus genome. Some vectors can replicate autonomously in the host cells that they are introduced in (for example, bacterial vectors with bacterial replication starting points and additive mammalian vectors). Other vectors (such as non-additive mammalian vectors) can be integrated into the host cell genome after being introduced into the host cell, then replicating together with the host genome. In addition, certain vectors can guide the expression of genes that can be operably connected to them. Usually, useful expression vector in recombinant DNA technology is typically in the form of plasmid.

[0109] The terms "IL-15" and "IL-15Ra" can refer to their mutants or fragments.

[0110] The terms "first" and "second" are only used for descriptive purposes and do not indicate or imply their degree of importance.

[0111] The present invention uses the existing CD3 antibody SP34 as the maternal antibody, mutates its variable region, and obtains a CD3 antibody variant. The present invention also provides several protein molecules with different configurations targeting different targets.

[0112] The sequence of "IL-15~IL15Ra" can be the following:

SEQ ID NO: 42

NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL

ELQVISCESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEE

LEEKNIKEFLQSFVHIVQMFINTSSGGGSGGGGSGGGGSGGGGSG

GGSGGITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTC

SLTECVLNKATNVAHWTTPSLKCIR.

[0113] The sequence of "IL-15Ra~IL-15" can be the following:

SEQ ID NO: 43

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTCSLTEC

VLNKATNVAHWTTPSLKCIRSGGSGGGGSGGGSGGGGSLQNWVNV

ISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVI

SCESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKN

IKEFLQSFVHIVQMFINTS.

I. Obtaining Anti-CD3 Antibody Variants and Design of an Anti-TAA (Tumor Associated Antigen)/CD3 Bispecific Antibody Format

Example 1: Obtaining, Molecular Cloning, Transient Expression, and Protein Purification of Anti-CD3 Antibody Variants

[0114] 1. Molecular cloning: Humanized anti-CD3 antibody SP34 (Wileman et al., 1990; U.S. Pat. No. 8,236,308) was used for further molecular engineering. Its CDRs were mutated and antibodies with high stability were screened, and three variants were obtained. A single chain antibody VH-VL was constructed by connecting the light and heavy chain variable regions of CD3 parent antibody SP34 and its variants by linkers, and fusing the FC segment of human IgG1 at C-terminus, then installed into the eukaryotic

expression vector pQD through molecular cloning. The clone numbers and protein sequence numbers are shown in the table below:

TABLE 1

Numbering of CD3 antibody SP34 and its mutant antibodies

Protein number	Clone number	Sequence number	Remark
QP3685	QD3685	SEQ ID NO: 01	hSP34 mutant VH-VL-FC
QP3689	QD3689	SEQ ID NO: 02	hSP34 mutant VH-VL-FC
QP3690	QD3690	SEQ ID NO: 03	hSP34 mutant VH-VL-FC
QP3679 (maternal antibody)	QD3679	SEQ ID NO: 04	hSP34 VH-VL-FC

[0115] The amino acid sequences are as follows:

SEQ ID NO:01 QD3685

EVQLLESGGGLVQPGGSLKLSCAASGFTFN**TYAMN**WVRQAPGKGLEWVA**RIRSKYNN**

YETYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR**HGNEGNSYVSWFAY**WG

QGTLVTVSS*GGGGSGGGGSGGGGS*ELVVTQEPSLTVSPGGTVTLTC**RSSTGAVTTSNYA**NW

VQQKPGQAPRGLIG**GTNLRAP**GTPARFSGSLLGGKAALTLSGVQPEDEAEYYC**ALWRSGG**

WVFGGGTKLTVLEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV

SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN

KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE

NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK.

SEQ ID NO:02 QD3689

EVQLLESGGGLVQPGGSLKLSCAASGFTFN**TYAMN**WVRQAPGKGLEWVA**RIRSKYNN**

YETYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR**HSNFGNGYVSWFAY**WG

QGTLVTVSS*GGGGSGGGGSGGGGS*ELVVTQEPSLTVSPGGTVTLTC**RSSTGAVTTSNYA**NW

VQQKPGQAPRGLIG**GTNLRAP**GTPARFSGSLLGGKAALTLSGVQPEDEAEYYC**ALWNKGG**

WVFGGGTKLTVLEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV

SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN

KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE

NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK.

SEQ ID NO:03 QD3690

EVQLLESGGGLVQPGGSLKLSCAASGFTFN**TYAMN**WVRQAPGKGLEWVA**RIRSKYNN**

YETYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR**HSNFGNGYVSWFAY**WG

QGTLVTVSS*GGGGSGGGGSGGGGS*ELVVTQEPSLTVSPGGTVTLTC**RSSTGAVTTSNYA**NW

VQQKPGQAPRGLIG**GTWLRAP**GTPARFSGSLLGGKAALTLSGVQPEDEAEYYC**ALWNSGG**

WVFGGGTKLTVLEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV

SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN

KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE

NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK.

-continued

SEQ ID NO:04 QD3679(hSP34 VH-VL-FC)

EVQLLESGGGLVQPGGSLKLSCAASGFTFN**TYAMN**WVRQAPGKGLEWVA**RIRSKYNN**

YATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR**HGNFGNSYVSWFAY**WG

QGTLVTVSS*GGGGSGGGGSGGGGS*ELVVTQEPSLTVSPGGTVTLTC**RSSTGAVTTSNYA**NW

VQQKPGQAPRGLIG**GTNKRAP**GTPARFSGSLLGGKAALTLSGVQPEDEAEYYC**ALWYSNL**

WVFGGGTKLTVLEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV

SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN

KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE

NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK.

[0116] Note: The underlined parts of amino acid sequences represent the heavy chain variable regions of the antibody, the parts with wavy line represent the light chain variable regions, and the italicized parts between the heavy chain variable region and the light chain variable region represent the linker sequence. The arrangement of acids in the amino variable region is FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4, with the bold and bottom highlighted parts representing HCDR1, HCDR3, HCDR3, LCDR1, LCDR2, and LCDR3, respectively. The comparison of maternal antibody and its mutant CDR sequences is shown in the table below:

TABLE 2

Comparison of maternal antibody and its mutant CDR sequences

Clone number	VHCDR1	VHCDR2	VHCDR3	VLCDR1	VLCDR2	VLCDR3
QD3679 (maternal antibody)	TYAM N (SEQ ID NO: 29)	RIRSKYNNYA TYYADSVKD (SEQ ID NO: 30)	HGNFGNSYVS WFAY (SEQ ID NO: 31)	RSSTGAVTTS NYA (SEQ ID NO: 32)	GTNKR AP (SEQ ID NO: 33)	ALWYSNL WV (SEQ ID NO: 34)
QD3685	TYAM N (SEQ ID NO: 29)	RIRSKYNNYE TYYADSVKD (SEQ ID NO: 35)	HGNFGNSYVS WFAY (SEQ ID NO: 31)	RSSTGAVTTS NYA (SEQ ID NO: 32)	GTNLR AP (SEQ ID NO: 37)	ALWRSGG WV (SEQ ID NO: 39)
QD3689	TYAM N (SEQ ID NO: 29)	RIRSKYNNYE TYYADSVKD (SEQ ID NO: 35)	HSNFGNGYVS WFAY (SEQ ID NO: 36)	RSSTGAVTTS NYA (SEQ ID NO: 32)	GTNLR AP (SEQ ID NO: 37)	ALWNKGG WV (SEQ ID NO: 40)
QD3690	TYAM N (SEQ ID NO: 29)	RIRSKYNNYE TYYADSVKD (SEQ ID NO: 35)	HSNFGNGYVS WFAY (SEQ ID NO: 36)	RSSTGAVTTS NYA (SEQ ID NO: 32)	GTWLR AP (SEQ ID NO: 38)	ALWNSGG WV (SEQ ID NO: 41)

[0117] 2. Protein expression: The cell density of 293E cells was adjusted to 1×10^6/ml. Plasmid and transfection reagent PEI were prepared, and the amount of plasmids to be transfected were 100 μg/100 mL of cells, and the mass ratio of PEI to plasmids was 2:1. The plasmids and PEI were mixed uniformly, then standing for 15 minutes. The mixture of plasmids and PEI was slowly added to 293E cells, and cultured in a shaker at 8% CO_2, 120 rpm and 37° C. On the fifth to sixth day of transfection, the cell supernatant was collected after being centrifuged in a horizontal centrifuge at 4700 rpm for 20 minutes for purification.

3. Protein Purification:

[0118] Protein affinity chromatography: the cell culture medium was subjected to high-speed centrifugation and the supernatant was obtained, and affinity chromatography was performed using GE Protein A chromatography column. The equilibrium buffer for chromatography was 1×PBS (pH7.4). After the cell supernatant was loaded and combined, the column was washed with PBS until the ultraviolet light returned to the baseline, then the target protein was eluted with 0.1M glycine (pH3.0), and preserved at a pH adjusted to neutral by Tris. Protein volume exclusion chromatography: the ion-exchange products were concentrated by ultrafiltration for volume exclusion chromatography. For example, GE Superdex200 gel was used for separation to remove possible polymers and other components to obtain

target products with high-purity. The purity analysis of the obtained protein can be performed through SDS-PAGE and SEC-HPLC detection. The protein concentration was determined by UV spectrophotometry.

[0119] The production and purity of the expressed protein by cells are shown in the table below. QP3679 is the maternal humanized anti-CD3 antibody SP34, with a production of 68.64 mg/L, and the mutant anti-CD3 antibody shows higher expression yield than the maternal antibody QP3679, indicating that the mutant has a higher yield and possibly better protein stability. At the same time, the SEC-HPLC detection shows that the protein purity is all good.

TABLE 3

Transient Production and Protein Purity of SP34 Antibodies and Their Variants

Clone number	Protein number	293E Transient Expression Production(mg/L)	SEC-HPLC Protein Purity (%)
QD3679 (maternal antibody)	QP3679	68.64	97.3
QD3685	QP3685	145.86	97.2
QD3689	QP3689	142.56	97.4
QD3690	QP3690	123.42	98.2

Example 2: FACS Detection of Anti-CD3 Antibody Variants Binding to Jurkat Cells Naturally Expressing CD3

[0120] FACS detection of anti-CD3 antibody binding activity: Human lymphocytic leukemia cells (Jurkat cells) express natural CD3. The binding of anti-CD3 antibodies and mutants thereof to Jurkat cells was detected by FACS (fluorescence activated cell sorter). The Jurkat cells were seeded into U-shaped 96-well plate with 1E5/well, washed with cold PBS, and centrifuged at 1200 rpm for 3 min. After washing, 3% FBS/PBS blocking buffer was added at 200 μL/well, and incubated on ice for 1 h. After blocking, centrifugation was performed at 1200 rpm for 3 min, and the supernatant was discarded. Samples with different concentrations were added for incubation on ice for 2 h, and washed with cold PBS for three times. PE-anti human FC antibody was added for incubation, which was diluted at a ratio of 1:200, added at 50 μl/well and mixed uniformly, then incubated on ice for 1 h, and washed with cold PBS for 3 times. Cells were resuspended by 200 μl/well PBS, and the average fluorescence values were read on FACS instruments. The results were analyzed using Graphpad prism software.

[0121] As shown in FIG. **1**, the activity of the anti-CD3 antibody SP34 and its mutants QP3685, QP3689, and QP3690 binding Jurkat cells were maintained.

Example 3: Design of an Anti-TAA (Tumor Associated Antigen) and Anti-CD3 Bispecific Antibody Format

[0122] The therapeutic effect of CD3 bispecific antibody is mainly achieved by simultaneously binding to tumor associated antigens (TAA) expressed on tumor cells and CD3 on T cells, cross-linking these two types of cells to form immune synapses, leading to T cell activation and killing tumor cells. Multivalent TAA antibodies can improve selectivity towards targets, especially when the targets are not specific enough. The main direction for improving the safety of CD3 bispecific antibody is to improve the selectivity of TAA, while selecting appropriate CD3 antibody affinity can maintain efficacy and reduce toxic side effects, thereby improving tumor selectivity and reducing targeting of healthy cells.

[0123] The molecular format design of the anti-TAA (tumor associated antigen) and anti-CD3 bispecific antibody provided by the present invention is shown in FIG. **2**.

[0124] The anti-TAA and anti-CD3 bispecific antibody molecule shown in FIG. **2** comprise: the first monomer (left side of FIG. **2**) and the second monomer (right side of FIG. **2**). The first monomer comprises two chains, namely chain 1, which has an Fd fragment comprising VH and CH1; and chain 2, which has a light chain fragment comprising VL and CL, and a first Fc chain. The second monomer also comprises two chains, namely chain 1, which has an Fd fragment comprising VH and CH1; and chain 2, which has a light chain fragment comprising VL and CL, an anti-CD3 antibody fragment (CD3 Antibody in scFv form in FIG. **2**), and a second Fc chain. In the first or second monomer, the light chain fragment and Fd fragment are paired to form the Fab domain against TAA (used to achieve the function of the TAA Antibody in FIG. **2**), respectively. Unlike conventional antibody, the light chain fragment of the first monomer is fused with the first Fc chain; meanwhile the N-terminus of the anti-CD3 antibody fragment is fused with the light chain fragment of the second monomer, and the C-terminus of the anti-CD3 antibody fragment is fused with the second Fc chain. The first Fc chain and the second Fc chain are polymerized to form an Fc domain. The Fc domain can be selected from Human IgG1 Fc, Human IgG2 Fc, Human IgG3 Fc, Human IgG4 Fc, or variants thereof.

Molecular Cloning, Transient Expression, and Protein Purification of Bispecific Antibody:

1. Molecular Cloning:

[0125] According to FIG. **2**, CLDN18.2 was selected as the TAA and an anti-CLDN18.2/CD3 bispecific antibody was designed. The anti-CLDN18.2 antibody sequence can be referred to the sequence of antibody QP14611463 in patent CN202010344676.8. The light chain and heavy chain sequences of SP34 and its variants QP3685, QP3689, and QP3690 were used as anti-CD3 antibody sequence, respectively. The anti-CD3 antibody sequence of QP374537493746 was SP34, and the anti-CD3 antibody sequences of QP090837493746, QP090937474746, and QP091037493746 were selected from QP3685, QP3689, and QP3690. The protein expression and sequence number are shown in the table below.

TABLE 4

Clone design of bispecific antibodies

Protein number	Clone number	Description	Sequence number
QP374537493746	QD3745	QD3745-pQD-anti18.2VL-CL-hSP34 VH-VL-Fc(Knob)	SEQ ID NO: 05

TABLE 4-continued

Clone design of bispecific antibodies

Protein number	Clone number	Description	Sequence number
	QD3749	QD3749-pQD-anti18.2VL-CL-Fc(Hole)	SEQ ID NO: 06
	QD3746	QD3746-pQD-antiClaudin18.2VH-CH1	SEQ ID NO: 07
QP090837493746	QD908	QD908-pQD-anti18.2VL-CL-hSP34 VH-VL(QD3685)-Fc(Knob)(QD3685)	SEQ ID NO: 08
	QD3749	QD3749-pQD-anti18.2VL-CL-Fc(Hole)	SEQ ID NO: 06
	QD3746	QD3746-pQD-antiClaudin18.2VH-CH1	SEQ ID NO: 07
QP090937493746	QD909	QD909-pQD-anti18.2VL-CL-hSP34 VH-VL(QD3689)-Fc(Knob)(QD3689)	SEQ ID NO: 09
	QD3749	QD3749-pQD-anti18.2VL-CL-Fc(Hole)	SEQ ID NO: 06
	QD3746	QD3746-pQD-antiClaudin18.2VH-CH1	SEQ ID NO: 07
QP091037493746	QD910	QD910-pQD-anti18.2VL-CL-hSP34 VH-VL(QD3690)-Fc(Knob)(QD3690)	SEQ ID NO: 10
	QD3749	QD3749-pQD-anti18.2VL-CL-Fc(Hole)	SEQ ID NO: 06
	QD3746	QD3746-pQD-antiClaudin18.2VH-CH1	SEQ ID NO: 07

[0126] At the same time, for comparison, two other forms of anti-CLDN18.2/CD3 bispecific antibody molecules QP372337241461 and QP374437481461 were constructed. According to patent US20200055932A1, CLDN18.2/CD3 bispecific antibody molecule AMG910 from Amgen was constructed, which was numbered QP3693. The protein expression and sequence number are shown in the table below.

TABLE 5

Molecular cloning of bispecific antibodies

Protein number	Clone number	Description	Sequence number
QP372337241461	QD3723	QD3723-pQD-anti18.2Fd-hSP34VH-G4Fc(Hole)	SEQ ID NO: 11
	QD3724	QD3724-pQD-anti18.2Fd-hSP34VL-G4Fc(Knob)	SEQ ID NO: 12
	QD1461	QD1461-anti18.2LC	SEQ ID NO: 13
QP374437481461	QD3744	QD3744-pQD-anti18.2Fd-hSP34VH.VL-G4Fc(Knob)	SEQ ID NO: 14
	QD3748	QD3748-pQD-anti18.2Fd(G1)-G4Fc(Hole)	SEQ ID NO: 15
	QD1461	QD1461-anti18.2LC	SEQ ID NO: 13
QP3693	QD3693	AMG910	SEQ ID NO: 16

[0127] The molecular format design of QP372337241461 is shown in FIG. **3**. The molecular format design of QP374437481461 is shown in FIG. **4**.

2. Clone Construction Method

[0128] Clones were designed and full-length expression vectors were constructed as shown in Tables 4 and 5. Primer design: The online software DNAWorks (v3.2.4) (http://helixweb.nih.gov/dnaworks/) was used to design a number of primers to synthesize fragments comprising the gene fragment needed for recombination. Fragment splicing: According to the operational instruction of Primer STAR GXL DNA polymerase from TaKaRa company, multiple primers designed above were used for PCR amplification, and the gene fragments needed for recombination were obtained. Step 1 PCR: 50 μL PCR reaction system comprising 10 μL PrimerSTAR GXL Buffer (5×); 4 μL dNTP Mixture (2.5 mmol·L−1); 1 μL each kind of above-mentioned primers; 1 μL Prime STAR GXL DNA Polymerase. The PCR reaction conditions were 98° C. for 2 minutes, 98° C. for 20 seconds, 55° C. for 15 seconds, 68° C. for 30 seconds, and 30 cycles; 68° C. for 5 minutes. Step 2 PCR: Using the PCR product in step 1 as a template, the forward and reverse primers were used for PCR amplification under the same conditions as the step 1. The target fragments were amplified by PCR. Construction and enzyme digestion of expression vector pQD: the characteristic of some special restriction endonucleases, such as BsmBI, that their recognition sequences differ from and the digestion site was used to design and construct expression vector pQD (with a signal peptide). The vector was digested by BsmBI enzyme, and the glue was cut and recovered for later use. Recombinant construction of expression vector: The recombinant target gene fragment and the expression vector pQD (with signal peptide fragments) recovered from BsmBI digestion were added to DH5a competent cells at a ratio of 3:1, and subjected to ice bath at 0° C. for 30 minutes, heat shock at 42° C. for 90 seconds, then added with 5 times the volume of LB medium, incubated at 37° C. for 45 minutes, coated to LB Amp plates, and cultured overnight at 37° C. Single clones were picked for sequencing to obtain various target clones.

3. Protein Expression

[0129] The density of 293E cells was adjusted to 1×10^6/ml. The plasmids and transfection reagent PEI were prepared, and the amount of plasmids to be transfected was 100 ug/100 ml cells. The mass ratio of PEI and plasmid is 2:1. The plasmids and PEI were mixed well, then standing for 15 minutes. The mixture of plasmids and PEI was slowly added to 293E cells, and cultured in a shaker at 8% CO_2, 120 rpm and 37° C. On the fifth to sixth day of transfection, the cell supernatant was collected after being centrifuged in a horizontal centrifuge at 4700 rpm for 20 minutes for purification.

4. Protein Purification:

[0130] Protein affinity chromatography: The cell culture medium was subjected to high-speed centrifugation and the supernatant was obtained, and affinity chromatography was performed using GE Protein A chromatography column. The equilibrium buffer for chromatography was 1×PBS (pH7.4). After the cell supernatant was loaded and combined, the column was washed with PBS until the ultraviolet light returned to the baseline, then the target protein was eluted with 0.1M glycine (pH3.0), and preserved at a pH adjusted to neutral by Tris. Protein volume exclusion chromatography: the ion-exchange products were concentrated by ultrafiltration for volume exclusion chromatography. For example, GE Superdex200 gel was used for separation to remove possible polymers and other components to obtain

target products with high-purity. The purity analysis of the obtained protein can be performed through SDS-PAGE and SEC-HPLC detection. The protein concentration was determined by UV spectrophotometry. The endotoxin was strictly controlled through entire purification process, and the endotoxin content of the purified protein was less than 1 EU/mg.

[0131] The results show that the CLDN18.2/CD3 bispecific antibodies QP374537493746, QP090837474746, QP090937474746, and QP091037493746 have high cell expression yield, and the purity of HPLC-SEC is higher than 95%, indicating producibility.

Example 4: FACS Detection of Bispecific Antibody Binding Activity to CLDN18.2

Experimental Steps

[0132] A cell line CHOS-CLDN18.2 with stable expression of CLDN18.2 were seeded into U-shaped 96-well plate with 1E5/well, washed with cold PBS, and centrifuged at 1200 rpm for 3 min. After washing, 3% FBS/PBS blocking buffer was added at 200 μL/well and incubated on ice for 1 h. After blocking, centrifugation was performed at 1200 rpm for 3 min, and the supernatant was discarded. Samples with different concentrations were added for incubation on ice for 2 h, and washed with cold PBS for three times. PE-anti human FC antibody was added for incubation, which was diluted at a ratio of 1:200, added at 50 μl/well, and mixed uniformly, then incubated on ice for 1 h, and washed with cold PBS for 3 times. Cells were resuspended by 200 μl/well PBS, and the average fluorescence values were read on FACS instruments. The results were analyzed using Graphpad prism software.

[0133] As shown in FIGS. **5** and **6**, the results show that anti-CLDN18.2/CD3 bispecific antibodies QP374537493746, QP090837493746, QP090937493746, and QP091037493746 all bind to CLDN18.2. As shown in FIG. **5**, the bispecific antibodies QP37453747493746, QP090837474746, QP090937474746, QP0909374746, and QP091037493746 in the form shown in FIG. **2** of the present invention have comparable binding affinity to the TAA target CLDN18.2 with the IgG form anti-CLDN18.2 antibody QP14611463, and significantly better than the control antibody AMG910 (1:1 form) QP3693, which meets the design expectation.

Example 5: FACS Detection of Bispecific Antibody and Binding Activity to CD3

[0134] Human lymphocytic leukemia cells (Jurkat cells) express natural CD3. The binding of anti-CD3 antibodies and mutants thereof to Jurkat cells was detected by FACS. The Jurkat cells were seeded into U-shaped 96-well plate with 1E5/well, washed with cold PBS, and centrifuged at 1200 rpm for 3 min. After washing, 3% FBS/PBS blocking buffer was added at 200 μL/well and incubated on ice for 1 h. After blocking, centrifugation was performed at 1200 rpm for 3 min, and the supernatant was discarded. Samples with different concentrations were added for incubation on ice for 2 h, and washed with cold PBS for three times. PE-anti human FC antibody was added for incubation, which was diluted at a ratio of 1:200, added at 50 μl/well, and mixed uniformly, then incubated on ice for 1 h, and washed with PBS for 3 times. Cells were resuspended by 200 μl/well PBS, and the average fluorescence values were read on FACS instruments. The results were analyzed using Graphpad prism software.

[0135] As shown in FIGS. **7** and **8**, the results show that anti-CLDN18.2/CD3 bispecific antibodies QP374537493746, QP090837493746, QP09093747493746, and QP091037493746 all bind to CD3. As shown in FIG. **7**, the bispecific antibodies QP374537493746, QP090837493746, QP090937474746, and QP091037493746 with the form shown in FIG. **2** of the present invention can be divided into two categories in terms of binding affinity to CD3. The binding affinity of QP374537493746 and QP090837493746 to CD3 is weaker, while the binding affinity of QP090937493746 and QP091037493746 is stronger. However, the binding affinity of these two categories of molecules to CD3 is weaker than that of the control antibody AMG910 (1:1 form) QP3693, which meets the expectation that lower affinity of CD3 antibodies will improve the safety of CD3 bispecific antibodies.

Example 6: Anti-CLDN18.2/CD3 Bispecific Antibody Mediated T Cell Killing of Human Gastric Cancer Cells

[0136] Experimental method: Human gastric cancer cell line NUGC4-CLDN18.2 stably expressing CLDN18.2 was selected as the target cells. The effector cells were human PBMCs. The E:T ratio was 10:1, and antibodies of different concentrations were added and incubated at 37° C., 5% CO_2 for 48 hours. CytoTox 96® Non-Radioactive Cytotoxicity Assay (Promega, G1780-1000 assays) was used to detect LDH in cell culture supernatant and quantify cytotoxicity %. The maximum lysis rate of target cells (100%) is that 1% Triton X-100 treatment of target cells causes cell lysis to release all LDH. Control wells were set for target cell spontaneity, effector cell spontaneity, and target cell+effector cell spontaneity. The data was analyzed according to the formula: % Cytotoxicity=[(Experimental Effector Spontaneous−Target Spontaneous)/(Target Maximum−Target Spontaneous)]×100.

[0137] As shown in FIGS. **9** and **10**, QP37453749374746, QP090837474746, QP090937474746, and QP091037493746 all mediate PBMC killing of human gastric cancer cells NUGC4-CLDN18.2. As shown in FIG. **9**, the activity of PBMC killing human gastric cancer cells NUGC4-CLDN18.2 mediated by the bispecific antibodies QP374537493746, QP090837474746, QP0909374746, and QP091037493746 in the form of FIG. **2** of the present invention were stronger than that of the control molecule QP3693 (AMG910). Although the binding affinity to CD3 of the selected CD3 antibody in the present invention is weaker than that of the CD3 antibody of AMG910 molecule (see FIG. **7**), it does not affect the killing ability against target cells.

Example 7: Anti-CLDN18.2/CD3 Bispecific Antibody Mediated T Cell Killing of Human Lung Cancer Cells

[0138] Experimental method: Human lung cancer cell line HCC827-CLDN18.2 stably expressing CLDN18.2 was selected as the target cells. The effector cells were human PBMCs. The E:T ratio was 10:1, and antibodies of different concentrations were added and incubated at 37° C., 5% CO_2

for 48 hours. CytoTox 96® Non-Radioactive Cytotoxicity Assay (Promega, G1780-1000 assays) was used to detect LDH in cell culture supernatant and quantify cytotoxicity %. The maximum lysis rate of target cells (100%) is that 1% Triton X-100 treatment of target cells causes cell lysis to release all LDH. Control wells were set for target cell spontaneity, effector cell spontaneity, and target cell+ effector cell spontaneity. The data was analyzed according to the formula: % Cytotoxicity=[(Experimental Effector Spontaneous-Target Spontaneous)/(Target Maximum-Target Spontaneous)]×100.

[0139] As shown in FIG. **11**, CD3 bispecific antibody molecules QP374537493747474746, QP090837474746, QP090937474746, and QP091037493746 all mediate PBMC killing of human lung cancer cells HCC827-CLDN18.2. The activity of PBMC killing human lung cancer cells HCC827-CLDN18.2 mediated by CD3 bispecific antibody molecules QP3745374747474746, QP090837474746, QP090937474746, and QP091037493746 in the form of FIG. **2** of the present invention were stronger than that of the control molecule QP3693 (AMG910). The results of NUGC4-CLDN18.2 were repeated on HCC827-CLDN18.2 cells (see FIG. **9**).

Example 8: Efficacy of Anti-CLDN18.2/CD3 Bispecific Antibodies in CD3 Humanized Mouse Model

[0140] The inhibitory effect of anti-CLDN18.2/CD3 bispecific antibody molecules on tumor growth was evaluated in the CD3 humanized mouse (CD3EDG HuGEMM) model. MC38-hCLDN18.2 colorectal cancer cells in exponential growth phase were collected, and resuspended in PBS to an appropriate concentration for inoculation. Each experimental mouse was subcutaneously inoculated on the right back with 5×10^6 MC38-hCLDN18.2 cells, and the growth of the tumor was regularly observed. When the tumor grew to an average volume of about 100 mm^3, the mice were randomly grouped and administered according to the tumor size and mouse weight. The dosage regimen is as follows:

TABLE 6

The dosage regimen to evaluate the inhibitory effect of anti-CLDN18.2/CD3 bispecific antibody molecules on tumor growth

		Number	Dosage		Administration	Dosing
Group	Administration	of mice	Drug	(mg/kg)	route	frequency
1	Vehicle	6	PBS	—	ip	BIW × 6
2	AMG910	6	AMG910	0.7	ip	BIW × 6
3	QP374537493746	6	QP374537493746	0.6	ip	BIW × 6
4	QP372337241461	6	QP372337241461	1.2	ip	BIW × 6
5	QP374437481461	6	QP374437481461	1.2	ip	BIW × 6

[0141] As the dosage regimen shown in the above table, the drugs were administered 6 times and the tumor was measured twice a week. The tumor growth inhibition rate is shown in Table 7, and the tumor inhibition curve is shown in FIG. **12**. The results show that on the 21st day after administration, the tumor growth inhibition rate (TGI) of QP374537493746 in the low dosage group of 0.6 mpk reaches 89.29%, which was better than or equivalent to the tumor growth inhibition rate (TGI=86.5%) of the control antibody AMG910 in the 0.7 mpk group (the molar concentration of AMG910 in 0.7 mpk group is equivalent to that of QP374537493746 1.2 mpk), indicating that half the dosage of QP374537493746 can achieve the same tumor growth inhibition effect as the control antibody AMG910. FIG. **13** shows the body weight changes of mice in each group after administration. The results show that the mice in the administration group remain basically unchanged body weight and grow well, indicating good drug safety.

TABLE 7

Inhibition of tumor growth by CLDN18.2/CD3 bispecific antibody molecules in an in vivo animal model of subcutaneous transplantation of colorectal cancer cells MC38-hCLDN18.2 in CD3EGD HuGEMM mice

		Mean Tumor volume (mm^3)				
Group	Treatment	(Mean ± SEM)/ grouping	(Mean ± SEM)/ Days post inoculation	% TGI (D21)	% T/C (D21)	P-Value (vs vehicle)
1	Vehicle, PBS, i.p., BIW × 6	78.50 ± 5.41(D0)	3014 ± 911.2(D21)	—	—	—

TABLE 7-continued

Inhibition of tumor growth by CLDN18.2/CD3 bispecific antibody molecules in an in vivo animal model of subcutaneous transplantation of colorectal cancer cells MC38-hCLDN18.2 in CD3EGD HuGEMM mice

Group	Treatment	Mean Tumor volume (mm^3) (Mean ± SEM)/ grouping	Mean Tumor volume (mm^3) (Mean ± SEM)/ Days post inoculation	% TGI (D21)	% T/C (D21)	P-Value (vs vehicle)
2	AMG910, 0.7 mpk, i.p., BIW × 6	78.76 ± 6.61(D0)	47 ± 394.02(D21)	86.50	13.50	0.0001
3	QP374537493746, 0.6 mpk, i.p., BIW × 6	78.71 ± 6.06(D0)	393.11 ± 510.1(D21)	89.29	10.71	0.0001
4	QP372337241461, 1.2 mpk, i.p., BIW × 6	78.77 ± 6.47(D0)	506.37 ± 429.05(D21)	85.43	14.57	0.0001
5	QP374437481461, 1.2 mpk, i.p., BIW × 6	78.67 ± 5.38(D0)	431.7 ± 274.4(D21)	87.97	12.03	0.0001

*Note:

% T/C = (delta T/delta C) × 100, % TGI = 100 − % T/C.

Example 9: Efficacy of Anti-CLDN18.2/CD3 Bispecific Antibodies in Humanized NOG Mouse Model

[0142] Experimental objective: To evaluate the in vivo efficacy of the test substance in PBMC humanized NOG mouse X-CLDN18.2/MIA PaCa-2 subcutaneous xenograft model. Cell culture: X-CLDN18.2/MIA PaCa-2 cells were cultured in vitro under the conditions of medium supplemented with 10% fetal bovine serum, at 37° C., 5% CO_2, and regularly passaged twice a week. When the cells maintained in an exponential growth phase and the cell survival rate was greater than 95%, the cells were collected, counted, and the percentage of live cells was calculated, then the cells were subjected to inoculation. Animal: NOG mice, female, 6-8 weeks old, weighing 18-20 grams. A total of 36 animals (24 plus 50%) are required for the experiment. Animals were provided by qualified suppliers. Tumor inoculation: $5*10^6$ X-CLDN18.2/MIA PaCa-2 and $2*10^6$ PBMC cells were co-inoculated on the right back of each mouse's neck. At the same time, the experimental animals were labeled with ear labels as the only confirmation mark for subsequent experiments. When the tumor grew and the average volume of the tumor reached approximately 60-100 mm^3, the mice were grouped randomly and administrated. The experimental grouping and dosage regimen are shown in Table 8.

TABLE 8

The dosage regimen to evaluate the inhibitory effect of anti-CLDN18.2/CD3 bispecific antibody molecules on tumor growth

Group	Administration	Number of mice	Dosage Drug	Dosage (mg/kg)	Administration route	Dosing frequency
1	Vehicle	6	PBS	—	iv	BIW × 5
2	AMG910	6	AMG910	5	iv	BIW × 5
3	QP374537493746	6	QP374537493746	8	iv	BIW × 5
4	QP372337241461	6	QP372337241461	4	iv	BIW × 5

[0143] As the dosage regimen shown in the above table, the drugs were administered 5 times and the tumor was measured twice a week. The tumor growth inhibition rate is shown in Table 9, and the tumor inhibition curve is shown in FIG. **14**. The results show that on the 15th day after administration, the tumor growth inhibition rate (TGI) of QP374537493746 reaches 92.3% in the low dosage group of 4 mpk, and the tumor growth inhibition rate (TGI) in the high dosage group of 8 mpk reaches 99.8%, both are significantly better than that of the control antibody AMG910 in the 5 mpk group (TGI-69.3%) (the molar concentration of AMG910 in the 5 mpk group is equivalent to that of QP374537493746 in the high-dose group of 8 mpk). FIG. **15** shows the body weight changes of mice in each group after administration. The results show that the mice in the administration group has basically no change body weight and grow well, indicating good drug safety.

TABLE 9

Inhibition of tumor growth by CLDN18.2/CD3 bispecific antibody molecules inhibits tumor growth in PBMC humanized NOG mouse X-CLDN18.2/MIA PaCa-2 subcutaneous xenograft model

Group	Treatment	Mean Tumor volume(mm^3) (Mean ± SEM)/ grouping	Mean Tumor volume(mm^3) (Mean ± SEM)/ Days post inoculation	% TGI (D15)	% T/C (D15)	P-Value (vs vehicle)
1	Vehicle, PBS, i.v., BIW × 5	89 ± 9(D0)	659.09 ± 77.03(D15)	—	—	—
2	QP374537493746, 4 mpk, i.v., BIW × 5	89 ± 9(D0)	133.17 ± 46.00(D15)	92.30	7.7	0.0002
3	QP374537493746, 8 mpk, i.v., BIW × 5	89 ± 8(D0)	89.89 ± 24.56(D15)	99.80	0.2	0.0001
4	AMG910, 5 mpk, i.p., BIW × 5	89 ± 10(D0)	264.12 ± 107.37(D15)	69.30	30.7	0.003

*Note:

% T/C = (delta T/delta C) × 100, % TGI = 100 − % T/C.

II. Design of Anti-Tumor Associated Antigen (TAA), Anti-CD3 Antibody, and Cytokine IL15/IL15Ra-Containing Multifunctional Fusion Protein

[0144] Although CD3 bispecific antibodies have shown great potential in hematological tumors, they still face some challenges in the treatment of solid tumors. CD3 bispecific antibody therapy is associated with T cell infiltration and immunosuppression in solid tumor tissue. When there are few infiltrating T cells, it is easy to develop resistance to CD3 bispecific antibody therapy. IL15 is a soluble cytokine that can activate T and NK cells and mediate their proliferation and survival. A multifunctional TAA/CD3/IL15 fusion protein is designed in the present invention, in which the cytokine IL15 component can stimulate the proliferation of immune cells comprising T cells, and alter the immune microenvironment of tumors.

Example 10: Structure Design of Anti-TAA (Tumor Associated Antigen), Anti-CD3, and IL-15/IL15Ra-Containing Multifunctional Fusion Protein

[0145] The present invention provides a number of anti-TAA (tumor associated antigen), anti-CD3, and IL 15/IL15Ra-containing multifunctional fusion proteins.

[0146] 1. The first type of multifunctional fusion protein can be seen in FIGS. **16** to **19**, and the fusion protein molecules comprise the first monomer (left part in the figure) and the second monomer (right part in the figure). The first monomer comprises two chains, namely chain 1, which has an Fd fragment (comprising VH and CH1); and chain 2, which has a light chain fragment (comprising VL and CL), a cytokine functional region (comprising IL 15 and IL15Ra), and a first Fc chain. The second monomer comprise two chains, namely chain 1, which has an Fd fragment (comprising VH and CH1); and chain 2, which has a light chain fragment (comprising VL and CL), an anti-CD3 antibody fragment (CD3 Antibody in scFv form in the figure), and a second Fc chain. In the first or second monomers, the light chain fragment and Fd fragment are paired to form the Fab domain of anti-TAA (used to achieve the function of anti-TAA antibody in the figure). The N-terminus of the cytokine functional region is fused with the light chain fragment of the first monomer, while the C-terminus is fused with the first Fc chain; the N-terminus of the anti-CD3 antibody fragment is fused with the light chain fragment of the second monomer, and the C-terminus is fused with the second Fc chain. The first Fc chain and the second Fc chain are polymerized to form an Fc domain.

[0147] In FIGS. **16** to **19**, the anti-CD3 antibody fragment in scFv form can comprise: a heavy chain variable region (VH), a light chain variable region (VL), and linker connecting the heavy chain variable region and light chain variable region. From the N-terminus to the C-terminus of the peptide chain, the fusion order of amino acids can be "VH (CD3)~VL (CD3)", or "VL (CD3)~VH (CD3)"; wherein "~" represents a linker. The fusion order of amino acid fragments in the cytokine functional region can be "IL-15~IL-15Ra", or "IL-15Ra~IL-15".

[0148] The four polypeptide chains of the fusion protein shown in FIG. **16** can be described as follows: (1) the first polypeptide chain: VH-CH1; (2) the second polypeptide chain: VL-CL-IL15Ra-IL15—the first Fc chain; (3) the third polypeptide chain: VL-CL-VH (CD3)-VL (CD3)—the second Fc chain; (4) the fourth polypeptide chain: VH-CH1. "-" represents connecting by a peptide bond or a linker.

[0149] The four polypeptide chains of the fusion protein shown in FIG. **17** are described as follows: (1) the first polypeptide chain: VH-CH1; (2) the second polypeptide chain: VL-CL-IL15-IL15Ra—the first Fc chain; (3) the third polypeptide chain: VL-CL-VH (CD3)-VL (CD3)-second Fc chain; (4) the fourth polypeptide chain: VH-CH1.

[0150] The four polypeptide chains of the fusion protein shown in FIG. **18** are described as follows: (1) the first polypeptide chain: VH-CH1; (2) the second polypeptide chain: VL-CL-IL15Ra-IL15—the first Fc chain; (3) The third polypeptide chain: VL-CL-VL (CD3) VH (CD3)-second Fc chain; (4) The fourth polypeptide chain: VH-CH1.

[0151] The four polypeptide chains of the fusion protein shown in FIG. **19** are described as follows: (1) the first polypeptide chain: VH-CH1; (2) The second polypeptide chain: VL-CL-IL15-IL15Ra—the first Fc chain; (3) The third polypeptide chain: VL-CL-VL (CD3) VH (CD3)—the second Fc chain; (4) The fourth polypeptide chain: VH-CH1.

[0152] 2. The second type of multifunctional fusion protein can be seen in FIGS. **20** to **27**, and the protein molecules comprise the first monomer (left part in the figure) and the second monomer (right part in the figure). The first monomer comprises: an anti-TAA antibody fragment (in scFv form, comprising VH and VL domains), a cytokine func-

tional region (comprising IL15 and IL 15Ra), and a first Fc chain; the second monomer comprises: an anti-TAA antibody fragment (in scFv form, comprising VH and VL domains), an anti-CD3 antibody fragment (CD3 Antibody in the figure in scFv form), and a second Fc chain. The N-terminus of the cytokine functional region is fused with the anti-TAA antibody fragment of the first monomer, while the C-terminus is fused with the first Fc chain; the N-terminus of the anti-CD3 antibody fragment is fused with the anti-TAA antibody fragment of the second monomer, and the C-terminus is fused with the second Fc chain. The first Fc chain and the second Fc chain are polymerized to form an Fc domain.

[0153] Similar to the first type of multifunctional fusion protein, the anti-CD3 antibody fragment in scFv form can comprise: a heavy chain variable region (VH), a light chain variable region (VL), and a linker connecting heavy chain variable region and light chain variable region. The fusion order of amino acids in the anti-CD3 antibody fragment from the N-terminus to the C-terminus of the peptide chain can be "VH (CD3)~VL (CD3)", or "VL (CD3)~VH (CD3)"; wherein "~" represents a linker. The fusion order of amino acid fragments in the cytokine functional region can be "IL-15~IL-15Ra", or "IL-15Ra~IL-15". In addition, the anti-TAA antibody fragment in scFv form comprises: a heavy chain variable region (VH), a light chain variable region (VL), and a linker connecting the heavy chain variable region and the light chain variable region; the amino acid fusion sequence of the anti-TAA antibody fragment from the N-terminus to the C-terminus of the peptide chain can be "VH (TAA)~VL (TAA)", or "VL (TAA)~VH (TAA)"; wherein "~" represents a linker.

[0154] The domains of the antibody molecules shown in FIGS. **20** to **27** share the same amino acid sequence, and differ in fusion order or configuration. Taking FIG. **20** as an example, the two polypeptide chains of the fusion protein are described as follows: (1) the first polypeptide chain: VL (TAA)-VH (TAA)-IL15-IL15Ra—the first Fc chain; (2) The second polypeptide chain: VL (TAA)-VH (TAA)-VH (CD3)-VL (CD3)—the second Fc chain.

[0155] 3. The present invention also provides a TAA/IL15 bifunctional fusion protein activated by tumor-targeted T/NK cell, whose structural form can be seen in FIG. **28**. Compared to the second type of multifunctional fusion protein, the difference is that the anti-CD3 antibody fragment is replaced with a cytokine functional region (comprising IL15 and IL15Ra). In FIG. **28**, the protein molecule has a symmetrical structural form.

Example 11: Molecular Cloning, Transient Expression, and Protein Purification of CLDN18.2/CD3/IL15 Multifunctional Fusion Protein

1. Molecular Cloning:

[0156] According to Example 10, a multifunctional fusion protein CLDN18.2/CD3/IL15 or CLDN18.2/IL15 was designed. For the CLDNI8.2 antibody, please refer to the sequence of the antibody QP14611463 in the patent document CN202010344676.8. The anti-CD3 antibody has uses SP34 light and heavy chain sequences. The protein expression and sequence numbers are shown in the table below.

TABLE 10

Clone design of multifunctional fusion proteins

Protein number	Clone number	Description	Sequence number
QP374508993746	QD3745	QD3745-pQD-anti18.2VL-CL-hSP34 VH-VL-Fc(Knob)	SEQ ID NO: 05
	QD0899	QD899-pQD-anti18.2VL-CL-IL15Ra-IL15-Fc(Hole)	SEQ ID NO: 17
	QD3746	QD3746-pQD-antiClaudin18.2VH-CH1	SEQ ID NO: 07
QP374509003746	QD3745	QD3745-pQD-anti18.2VL-CL-hSP34 VH-VL-Fc(Knob)	SEQ ID NO: 01
	QD0900	QD900-pQD-anti18.2VL-CL-IL15-IL15Ra-Fc(Hole)	SEQ ID NO: 18
	QD3746	QD3746-pQD-antiClaudin18.2VH-CH1	SEQ ID NO: 07
QP090108993746	QD0901	QD901-pQD-anti18.2VL-CL-hSP34 VL-VH-Fc(Knob)	SEQ ID NO: 19
	QD0899	QD899-pQD-anti18.2VL-CL-IL15Ra-IL15-Fc(Hole)	SEQ ID NO: 17
	QD3746	QD3746-pQD-antiClaudin18.2VH-CH1	SEQ ID NO: 07
QP090109003746	QD0901	QD901-pQD-anti18.2VL-CL-hSP34 VL-VH-Fc(Knob)	SEQ ID NO: 19
	QD0900	QD900-pQD-anti18.2VL-CL-IL15-IL15Ra-Fc(Hole)	SEQ ID NO: 18
	QD3746	QD3746-pQD-antiClaudin18.2VH-CH1	SEQ ID NO: 07
QP36673668	QD3667	QD3667-antiCLDN18.2 VL-VH-IL15-IL15Ra-IgG4 FC(Hole)-flag:	SEQ ID NO: 20
	QD3668	QD3668-antiCLDN18.2 VL-VH-Hsp34 VH-VL-IgG4 FC(Knob)-his:	SEQ ID NO: 21
QP09023668	QD0902	QD902-antiCLDN18.2 VL-VH-IL15Ra-IL15-IgG4 FC(Hole)-flag:	SEQ ID NO: 22
	QD3668	QD3668-antiCLDN18.2 VL-VH-Hsp34 VH-VL-IgG4 FC(Knob)-his:	SEQ ID NO: 21
QP36670903	QD3667	QD3667-antiCLDN18.2 VL-VH-IL15-IL15Ra-IgG4 FC(Hole)-flag:	SEQ ID NO: 20
	QD0903	QD903-antiCLDN18.2 VL-VH-Hsp34 VL-VH-IgG4 FC(Knob)-his:	SEQ ID NO: 23
QP09020903	QD0902	QD902-antiCLDN18.2 VL-VH-IL15Ra-IL15-IgG4 FC(Hole)-flag:	SEQ ID NO: 22
	QD0903	QD903-antiCLDN18.2 VL-VH-Hsp34 VL-VH-IgG4 FC(Knob)-his:	SEQ ID NO: 23
QP09040905	QD0904	QD904-antiCLDN18.2 VH-VL-IL15-IL15Ra-IgG4 FC(Hole)-flag:	SEQ ID NO: 24
	QD0905	QD905-antiCLDN18.2 VH-VL-Hsp34 VH-VL-IgG4 FC(Knob)-his:	SEQ ID NO: 25
QP09060905	QD0906	QD906-antiCLDN18.2 VH-VL-IL15Ra-IL15-IgG4 FC(Hole)-flag:	SEQ ID NO: 26
	QD0905	QD905-antiCLDN18.2 VH-VL-Hsp34 VH-VL-IgG4 FC(Knob)-his:	SEQ ID NO: 25
QP09040907	QD0904	QD904-antiCLDN18.2 VH-VL-IL15-IL15Ra-IgG4 FC(Hole)-flag:	SEQ ID NO: 24
	QD0907	QD907-antiCLDN18.2 VH-VL-Hsp34 VL-VH-IgG4 FC(Knob)-his:	SEQ ID NO: 27
QP09060907	QD0906	QD906-antiCLDN18.2 VH-VL-IL15Ra-IL15-IgG4 FC(Hole)-flag:	SEQ ID NO: 26
	QD0907	QD907-antiCLDN18.2 VH-VL-Hsp34 VL-VH-IgG4 FC(Knob)-his:	SEQ ID NO: 27

TABLE 10-continued

Clone design of multifunctional fusion proteins

Protein number	Clone number	Description	Sequence number
QP728	QD0728	QD728-Pqd-CLDN18.2 VL-VH-IL15-IL15Ra-FC(IgG4)	SEQ ID NO: 28

[0157] At the same time, the IL15/IL15Ra-Fc of Jiangsu Hengrui Pharmaceuticals Co., Ltd. was constructed as a control, and the IL15/IL15Ra-Fc protein was numbered QP33123313.

[0158] Clones were designed according to Table 10 and full-length expression vectors were constructed. The methods for clone construction, protein expression, and protein purification can be found in Example 3.

Example 12: FACS Detection of the Binding Activity of CLDN18.2/CD3/IL15 Multifunctional Fusion Protein to CLDN18.2

[0159] Experimental steps: A cell line CHOS-CLDN18.2 with stable expression of CLDN18.2 were seeded into U-shaped 96-well plate with 1E5/well, washed with cold PBS, and centrifuged at 1200 rpm for 3 min. After washing, 3% FBS/PBS blocking buffer was added at 200 μL/well and incubated on ice for 1 h. After blocking, centrifugation was performed at 1200 rpm for 3 min, and the supernatant was discarded. Samples with different concentrations were added for incubation on ice for 2 h, and washed with cold PBS for three times. PE-anti human FC antibody was added for incubation, which was diluted at a ratio of 1:200, added at 50 μl/well, and mixed uniformly, then incubated on ice for 1 h, and washed with cold PBS for 3 times. Cells were resuspended by 200 μl/well PBS, and the average fluorescence values were read on FACS instruments. The results were analyzed using Graphpad prism software. As shown in FIG. **29** and FIG. **30**, the results show that both CLDN18.2/CD3/IL15 and CLDN18.2/IL15 multifunctional fusion proteins bind to the TAA target CLDN18.2, and their affinity is better than that of the AMG910 analog (1:1 form) QP3693, which is in line with expectations.

Example 13: FACS Detection of the Binding Activity CLDN18.2/CD3/IL15 Multifunctional Fusion Protein to CD3

[0160] Human lymphocytic leukemia cells (Jurkat cells) express natural CD3. The binding of anti-CD3 antibodies and mutants thereof to Jurkat cells was detected by FACS. The Jurkat cells were seeded into U-shaped 96-well plate with 1E5/well, washed with cold PBS, and centrifuged at 1200 rpm for 3 min. After washing, 3% FBS/PBS blocking buffer was added at 200 μL/well and incubated on ice for 1 h. After blocking, centrifugation was performed at 1200 rpm for 3 min, and the supernatant was discarded. Samples with different concentrations were added for incubation on ice for 2 h, and washed with cold PBS for three times. PE-anti human FC antibody was added for incubation, which was diluted at a ratio of 1:200, added at 50 μl/well, and mixed uniformly, then incubated on ice for 1 h, and washed with cold PBS for 3 times. Cells were resuspended by 200 μl/well PBS, and the average fluorescence values were read on FACS instruments. The results were analyzed using Graphpad prism software. As shown in FIGS. **31** and **32**, the results show that all CLDN18.2/CD3/IL15 multifunctional fusion protein bind to CD3 with a weaker affinity than the control molecule AMG910 (QP3693). This is consistent with the inventor's expectation that the low affinity of CD3 antibodies will improve the safety of CD3 bispecific antibodies.

Example 14: Evaluation of the Activity of Multifunctional Fusion Protein IL15 by Mo7e Cell Proliferation Assay

[0161] Mo7e (human giant cell leukemia cell line) is a cytokine growth dependent cell expressing IL-15Rβγ. Previous studies have shown that resting NK and naïve T cells express moderate affinity IL-15Rβγ phenotype, and the results of cytokine IL15/IL15Ra on the proliferation of Mo7e (IL-15Rβγ) cells are consistent with those of unstimulated PBMC cells (Mol Cancer Ther; 11 (6) June 2012). Mo7e cell proliferation assay was used in the present invention to evaluate the activity of multifunctional fusion protein IL 15. The method and results are as follows:

[0162] Experimental reagent: Mo7e cells (human giant cell leukemia cell line) were purchased from the Cell Resource Center of the Institute of Basic Medicine, Chinese Academy of Medical Sciences; Cell Proliferation and Toxicity Test Kit (CCK-8) were purchased from Mei lun Biotech, catalog number MA0218; recombinant human GM-CSF was purchased from Properotech, catalog number 300-03; human IgG was purchased from Sigma, catalog number 14506; and other antibodies come from internal preparation.

[0163] Experimental method: Mole cells were cultured with RPMI1640 medium comprising 10% FBS, 2 mM L-glutamine, and 8 ng/ml GM-CSF in a 5% CO_2 incubator at 37° C.; Mole cells were collected, and centrifuged at 800 rpm for 5 minutes to discard the supernatant. The cells were washed twice with RPMI1640 culture medium without GM-CSF, and resuspended in RPMI1640 culture medium without GM-CSF and counted, then seeded in a 96 well plate at 2×10+ cells, 80 μl per well, and incubated in a 5% CO_2 incubator at 37° C. for 1 hour. Each medicinal culture medium to be tested was diluted with 4 times for gradients, added at 20 μl per cell and mixed well with cell suspension, then incubated in a 5% CO_2 incubator at 37° C. for 3 days; CCK-8 reagent was added to the 96 well plate 10 μl per well, and incubated in a 5% CO_2 incubator at 37° C. for 4 hours; The 96 well plate was taken out and the absorbance value was measured at a wavelength of 450 nm in a microplate reader.

[0164] The experimental results are shown in FIG. **33**, FIG. **34** and FIG. **35**. The results show that CLDN18.2/CD3/IL15 and CLDN18.2/IL15 multifunctional fusion proteins with different forms all have IL15 activity, and the activity varies from strong to weak according to different molecular designs. Different formats of construction produce molecules with different IL15 activity, which provides an opportunity to select the best therapeutic window.

Example 15: CLDN18.2/CD3/IL15 Multifunctional Fusion Protein Mediated T Cell Killing of Human Gastric Cancer Cells

[0165] Experimental method: Human gastric cancer cell line NUGC4-CLDN18.2 stably expressing CLDN18.2 was selected as the target cells. The effector cells were human PBMCs. The E:T ratio was 10:1, and antibodies of different

concentrations were added and incubated at 37° C., 5% CO_2 for 48 hours. CytoTox 96® Non-Radioactive Cytotoxicity Assay (Promega, G1780-1000 assays) was used to detect LDH in cell culture supernatant and quantify cytotoxicity %. The maximum lysis rate of target cells (100%) is that 1% Triton X-100 treatment of target cells causes cell lysis to release all LDH. Control wells were set for target cell spontaneity, effector cell spontaneity, and target cell+ effector cell spontaneity. The data was analyzed according to the formula: % Cytotoxicity=[(Experimental Effector Spontaneous-Target Spontaneous)/(Target Maximum-Target Spontaneous)]×100. The results are shown in FIG. **36** and FIG. **37**. QP374508993746, QP090109003746, QP09023688, QP36670903, QP09040905, QP09060905, QP09040907 and QP09060907 all can mediate PBMC to kill human gastric cancer cell NUGC4-CLDN 18.2 cells. Among them, the activity of PBMC killing the human gastric cancer cell NUGC4-CLDN18.2 mediated by QP374508993746 and QP090109003746 was significantly better than that of control molecule AMG910. The activity of PBMC killing the human gastric cancer cell NUGC4-CLDN18.2 mediated by other molecules was comparable to that of control molecule AMG910.

Example 16: CLDN18.2/CD3/IL15 Multifunctional Fusion Protein Mediated T Cell Killing of Human Lung Cancer Cells

[0166] Experimental method: Human lung cancer cell line HCC827-CLDN18.2 stably expressing CLDN18.2 was selected as the target cells. The effector cells were human PBMCs. The ET ratio was 10:1, and antibodies of different concentrations were added and incubated at 37° C., 5% CO_2 for 48 hours. CytoTox 96® Non-Radioactive Cytotoxicity Assay (Promega, G1780-1000 assays) was used to detect LDH in cell culture supernatant and quantify cytotoxicity %. The maximum lysis rate of target cells (100%) is that 1% Triton X-100 treatment of target cells causes cell lysis to release all LDH. Control wells were set for target cell spontaneity, effector cell spontaneity, and target cell+ effector cell spontaneity. The data was analyzed according to the formula: % Cytotoxicity=[(Experimental Effector Spontaneous−Target Spontaneous)/(Target Maximum−Target Spontaneous)]×100. As shown in FIG. **38**, the results show that QP090109003746, QP36670903, QP09040905, QP09060905 and QP09040907 all have the activity of mediating PBMC to kill human lung cancer cell HCC827-CLDN18.2. Among them, the activity of PBMC killing human lung cancer cell HCC827-CLDN18.2 mediated by QP090109003746 was significantly better than that of control molecule AMG910. The activity of PBMC killing human lung cancer cell HCC827-CLDN18.2 mediated by other molecules was comparable to that of control molecule AMG910.

[0167] In addition, in some other embodiments, the anti-CD3 antibody fragment was selected from the antibody light and heavy chain sequences of SP34 variants QP3685, QP3689, and QP3690 respectively, and the proteins were designed, cloned, expressed, and purified as shown in Table 10 of Example 11. The results show that the molecules constructed using the light and heavy chain sequences of QP3685, QP3689 and QP3690 also have CLDN18.2 binding activity and IL15 activity, while the anti-CD3 molecules also have CD3 binding activity, and have the effect of mediating T cells to kill human gastric cancer cells or lung cancer cells.

[0168] Although the contents of the present invention have been described in detail with reference to the above preferred embodiments, it should be recognized that the above description should not be considered a limitation of the present invention. Various modifications and alternatives to the present invention will be obvious to those skilled in the art upon reading the foregoing. Therefore, the scope of protection of the present invention shall be limited by the appended claims.

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

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Glu 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

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95
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Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
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Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn
                165                 170                 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190

Thr Asn Leu Arg Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Arg Ser Gly Gly Trp Val Phe
225                 230                 235                 240

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

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
            260                 265                 270

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        275                 280                 285

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    290                 295                 300

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305                 310                 315                 320

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                325                 330                 335

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            340                 345                 350

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
        355                 360                 365

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    370                 375                 380

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
385                 390                 395                 400

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                405                 410                 415

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            420                 425                 430

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        435                 440                 445

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480

Lys
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<210> SEQ ID NO 2
<211> LENGTH: 481
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3689

<400> SEQUENCE: 2

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

Ser Leu Lys 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

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Glu 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

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

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

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Val
130 135 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145 150 155 160

Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn
165 170 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
180 185 190

Thr Asn Leu Arg Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
195 200 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
210 215 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Asn Lys Gly Gly Trp Val Phe
225 230 235 240

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

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
260 265 270

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
275 280 285

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
290 295 300

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305 310 315 320

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
325 330 335

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
340 345 350

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys

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        355                 360                 365

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    370                 375                 380

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
385                 390                 395                 400

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                405                 410                 415

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            420                 425                 430

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        435                 440                 445

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480

Lys


<210> SEQ ID NO 3
<211> LENGTH: 481
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3690

<400> SEQUENCE: 3

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

Ser Leu Lys 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

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Glu 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

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

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

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn
                165                 170                 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190

Thr Trp Leu Arg Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220
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Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Asn Ser Gly Gly Trp Val Phe
225                 230                 235                 240

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

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
            260                 265                 270

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        275                 280                 285

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    290                 295                 300

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305                 310                 315                 320

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                325                 330                 335

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            340                 345                 350

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
        355                 360                 365

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    370                 375                 380

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
385                 390                 395                 400

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                405                 410                 415

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            420                 425                 430

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        435                 440                 445

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480

Lys


<210> SEQ ID NO 4
<211> LENGTH: 481
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3679 (hSP34 VH-VL-FC)

<400> SEQUENCE: 4

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

Ser Leu Lys 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

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 Thr
65                  70                  75                  80
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Ala Tyr Leu Gln Met Asn Asn 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 Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn
                165                 170                 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190

Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Leu Trp Val Phe
225                 230                 235                 240

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

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
            260                 265                 270

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        275                 280                 285

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    290                 295                 300

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305                 310                 315                 320

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                325                 330                 335

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            340                 345                 350

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
        355                 360                 365

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    370                 375                 380

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
385                 390                 395                 400

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                405                 410                 415

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            420                 425                 430

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        435                 440                 445

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480

Lys
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<210> SEQ ID NO 5
<211> LENGTH: 740
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3745

<400> SEQUENCE: 5

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
20 25 30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
35 40 45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
50 55 60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
100 105 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
115 120 125

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

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

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
165 170 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
180 185 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
195 200 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
210 215 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly
225 230 235 240

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser
245 250 255

Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala
260 265 270

Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp Val Arg Gln
275 280 285

Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr
290 295 300

Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr
305 310 315 320

Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn
325 330 335

Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn
340 345 350

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Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
        355                 360                 365

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    370                 375                 380

Gly Gly Gly Gly Ser Glu Leu Val Val Thr Gln Glu Pro Ser Leu Thr
385                 390                 395                 400

Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly
                405                 410                 415

Ala Val Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly
            420                 425                 430

Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly
        435                 440                 445

Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu
    450                 455                 460

Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala
465                 470                 475                 480

Leu Trp Tyr Ser Asn Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr
                485                 490                 495

Val Leu Gly Gly Gly Gly Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro
            500                 505                 510

Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
        515                 520                 525

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    530                 535                 540

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
545                 550                 555                 560

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                565                 570                 575

Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            580                 585                 590

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        595                 600                 605

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
    610                 615                 620

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
625                 630                 635                 640

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
                645                 650                 655

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            660                 665                 670

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        675                 680                 685

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
    690                 695                 700

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
705                 710                 715                 720

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Ser Ser His His
                725                 730                 735

His His His His
            740
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<210> SEQ ID NO 6
<211> LENGTH: 478
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3749

<400> SEQUENCE: 6

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
20 25 30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
35 40 45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
50 55 60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
100 105 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
115 120 125

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

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

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
165 170 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
180 185 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
195 200 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
210 215 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu
225 230 235 240

Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu
245 250 255

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

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
275 280 285

Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
290 295 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
305 310 315 320

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
325 330 335

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser
340 345 350

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Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                405                 410                 415

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Arg Leu Thr
            420                 425                 430

Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460

Ser Leu Gly Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys
465                 470                 475


<210> SEQ ID NO 7
<211> LENGTH: 242
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3746

<400> SEQUENCE: 7

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
                85                  90                  95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
145                 150                 155                 160

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
    210                 215                 220
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Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
225 230 235 240

Ser Cys

<210> SEQ ID NO 8
<211> LENGTH: 740
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD908

<400> SEQUENCE: 8

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
20 25 30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
35 40 45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
50 55 60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
100 105 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
115 120 125

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

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

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
165 170 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
180 185 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
195 200 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
210 215 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly
225 230 235 240

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser
245 250 255

Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala
260 265 270

Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp Val Arg Gln
275 280 285

Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr
290 295 300

Asn Asn Tyr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr
305 310 315 320

Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn

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               325                 330                 335

Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn
            340                 345                 350

Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
        355                 360                 365

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    370                 375                 380

Gly Gly Gly Gly Ser Glu Leu Val Val Thr Gln Glu Pro Ser Leu Thr
385                 390                 395                 400

Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly
                405                 410                 415

Ala Val Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly
            420                 425                 430

Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Asn Leu Arg Ala Pro Gly
        435                 440                 445

Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu
    450                 455                 460

Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala
465                 470                 475                 480

Leu Trp Arg Ser Gly Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr
                485                 490                 495

Val Leu Gly Gly Gly Gly Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro
            500                 505                 510

Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
        515                 520                 525

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    530                 535                 540

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
545                 550                 555                 560

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                565                 570                 575

Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            580                 585                 590

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        595                 600                 605

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
    610                 615                 620

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
625                 630                 635                 640

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
                645                 650                 655

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            660                 665                 670

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        675                 680                 685

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
    690                 695                 700

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
705                 710                 715                 720

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Ser Ser His His
                725                 730                 735
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His His His His
            740


<210> SEQ ID NO 9
<211> LENGTH: 740
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD909

<400> SEQUENCE: 9

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

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

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

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly
225                 230                 235                 240

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser
                245                 250                 255

Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala
            260                 265                 270

Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp Val Arg Gln
        275                 280                 285

Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr
    290                 295                 300

Asn Asn Tyr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr
305                 310                 315                 320

Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn
                325                 330                 335
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Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Ser Asn
            340                 345                 350

Phe Gly Asn Gly Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
        355                 360                 365

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    370                 375                 380

Gly Gly Gly Gly Ser Glu Leu Val Val Thr Gln Glu Pro Ser Leu Thr
385                 390                 395                 400

Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly
                405                 410                 415

Ala Val Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly
            420                 425                 430

Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Asn Leu Arg Ala Pro Gly
        435                 440                 445

Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu
    450                 455                 460

Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala
465                 470                 475                 480

Leu Trp Asn Lys Gly Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr
                485                 490                 495

Val Leu Gly Gly Gly Gly Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro
            500                 505                 510

Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
        515                 520                 525

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    530                 535                 540

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
545                 550                 555                 560

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                565                 570                 575

Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            580                 585                 590

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        595                 600                 605

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
    610                 615                 620

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
625                 630                 635                 640

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
                645                 650                 655

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            660                 665                 670

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        675                 680                 685

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
    690                 695                 700

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
705                 710                 715                 720

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Ser Ser His His
                725                 730                 735
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His His His His
            740


<210> SEQ ID NO 10
<211> LENGTH: 740
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD910

<400> SEQUENCE: 10

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

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

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

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly
225                 230                 235                 240

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser
                245                 250                 255

Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala
            260                 265                 270

Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp Val Arg Gln
        275                 280                 285

Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr
    290                 295                 300

Asn Asn Tyr Glu Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr
305                 310                 315                 320

Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn
                325                 330                 335
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Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Ser Asn
            340                 345                 350

Phe Gly Asn Gly Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr
        355                 360                 365

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    370                 375                 380

Gly Gly Gly Gly Ser Glu Leu Val Val Thr Gln Glu Pro Ser Leu Thr
385                 390                 395                 400

Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly
                405                 410                 415

Ala Val Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly
            420                 425                 430

Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Trp Leu Arg Ala Pro Gly
        435                 440                 445

Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu
    450                 455                 460

Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala
465                 470                 475                 480

Leu Trp Asn Ser Gly Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr
                485                 490                 495

Val Leu Gly Gly Gly Gly Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro
            500                 505                 510

Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
        515                 520                 525

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    530                 535                 540

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
545                 550                 555                 560

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                565                 570                 575

Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            580                 585                 590

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        595                 600                 605

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
    610                 615                 620

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
625                 630                 635                 640

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
                645                 650                 655

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            660                 665                 670

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        675                 680                 685

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
    690                 695                 700

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
705                 710                 715                 720

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Ser Ser His His
                725                 730                 735

His His His His
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740

<210> SEQ ID NO 11
<211> LENGTH: 636
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3723

<400> SEQUENCE: 11

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
50 55 60

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65 70 75 80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
85 90 95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
115 120 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
130 135 140

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
145 150 155 160

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
165 170 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
180 185 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
195 200 205

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
210 215 220

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
225 230 235 240

Ser Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
245 250 255

Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
260 265 270

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr
275 280 285

Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
290 295 300

Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala
305 310 315 320

Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn
325 330 335

Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val

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            340                 345                 350

Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp
        355                 360                 365

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    370                 375                 380

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ser Lys
385                 390                 395                 400

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
                405                 410                 415

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            420                 425                 430

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
        435                 440                 445

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    450                 455                 460

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
465                 470                 475                 480

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
                485                 490                 495

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
            500                 505                 510

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        515                 520                 525

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    530                 535                 540

Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
545                 550                 555                 560

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
                565                 570                 575

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Arg Leu Thr Val Asp
            580                 585                 590

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
        595                 600                 605

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
    610                 615                 620

Gly Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys
625                 630                 635


<210> SEQ ID NO 12
<211> LENGTH: 618
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3724

<400> SEQUENCE: 12

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
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    50                  55                  60

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
                85                  90                  95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
145                 150                 155                 160

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
    210                 215                 220

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
225                 230                 235                 240

Ser Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                245                 250                 255

Ser Glu Leu Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
            260                 265                 270

Gly Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr
        275                 280                 285

Ser Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
    290                 295                 300

Gly Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg
305                 310                 315                 320

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
                325                 330                 335

Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser
            340                 345                 350

Asn Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
        355                 360                 365

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ser Lys
    370                 375                 380

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly
385                 390                 395                 400

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                405                 410                 415

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
            420                 425                 430

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        435                 440                 445

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
    450                 455                 460
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Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
465                 470                 475                 480

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
                485                 490                 495

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            500                 505                 510

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        515                 520                 525

Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    530                 535                 540

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
545                 550                 555                 560

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
                565                 570                 575

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
            580                 585                 590

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
        595                 600                 605

Gly Gly Ser Ser His His His His His His
    610                 615


<210> SEQ ID NO 13
<211> LENGTH: 242
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD1461

<400> SEQUENCE: 13

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15

Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser
            20                  25                  30

Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser
        35                  40                  45

Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr
    50                  55                  60

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser
65                  70                  75                  80

Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly
                85                  90                  95

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
            100                 105                 110

Val Tyr Tyr Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln
        115                 120                 125

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

Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
145                 150                 155                 160

Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
                165                 170                 175

Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
            180                 185                 190
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Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
        195                 200                 205

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
    210                 215                 220

Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
225                 230                 235                 240

Glu Cys


<210> SEQ ID NO 14
<211> LENGTH: 743
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3744

<400> SEQUENCE: 14

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
                85                  90                  95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
145                 150                 155                 160

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
    210                 215                 220

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
225                 230                 235                 240

Ser Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
                245                 250                 255

Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu
            260                 265                 270

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
        275                 280                 285
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Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
    290                 295                 300

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
305                 310                 315                 320

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
                325                 330                 335

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
            340                 345                 350

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
        355                 360                 365

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    370                 375                 380

Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Val Thr Gln Glu Pro
385                 390                 395                 400

Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Arg Ser
                405                 410                 415

Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln Gln
            420                 425                 430

Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Asn Lys Arg
        435                 440                 445

Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys
    450                 455                 460

Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr
465                 470                 475                 480

Tyr Cys Ala Leu Trp Tyr Ser Asn Leu Trp Val Phe Gly Gly Gly Thr
                485                 490                 495

Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Glu Ser Lys Tyr Gly Pro
            500                 505                 510

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
        515                 520                 525

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
    530                 535                 540

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
545                 550                 555                 560

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
                565                 570                 575

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
            580                 585                 590

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
        595                 600                 605

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
    610                 615                 620

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
625                 630                 635                 640

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu
                645                 650                 655

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
            660                 665                 670

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
        675                 680                 685

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
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    690                 695                 700

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
705                 710                 715                 720

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Ser
                725                 730                 735

Ser His His His His His His
            740


<210> SEQ ID NO 15
<211> LENGTH: 481
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3748

<400> SEQUENCE: 15

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
                85                  90                  95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
    130                 135                 140

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
145                 150                 155                 160

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
                165                 170                 175

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
            180                 185                 190

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
        195                 200                 205

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
    210                 215                 220

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
225                 230                 235                 240

Ser Cys Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
                245                 250                 255

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            260                 265                 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        275                 280                 285

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
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    290                 295                 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
305                 310                 315                 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                325                 330                 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
            340                 345                 350

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        355                 360                 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
    370                 375                 380

Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp
385                 390                 395                 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                405                 410                 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser
            420                 425                 430

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
        435                 440                 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    450                 455                 460

Leu Ser Leu Ser Leu Gly Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp
465                 470                 475                 480

Lys


<210> SEQ ID NO 16
<211> LENGTH: 990
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3693

<400> SEQUENCE: 16

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20                  25                  30

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

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Lys Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Asp Arg Ile Thr Val Ala Gly Thr Tyr Tyr Tyr Tyr Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met
    130                 135                 140

Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160
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Ile Thr Cys Arg Ala Ser Gln Gly Val Asn Asn Trp Leu Ala Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Thr Ala Ser
            180                 185                 190

Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Thr Asp Phe Thr Leu Thr Ile Arg Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220

Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Ile Thr Phe Gly Cys
225                 230                 235                 240

Gly Thr Arg Leu Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Val Gln
                245                 250                 255

Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys
            260                 265                 270

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn
        275                 280                 285

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile
    290                 295                 300

Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys
305                 310                 315                 320

Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu
                325                 330                 335

Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val
            340                 345                 350

Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp
        355                 360                 365

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
    370                 375                 380

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu
385                 390                 395                 400

Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly
                405                 410                 415

Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln
            420                 425                 430

Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe
        435                 440                 445

Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly
    450                 455                 460

Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu
465                 470                 475                 480

Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly
                485                 490                 495

Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys
            500                 505                 510

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
        515                 520                 525

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
    530                 535                 540

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
545                 550                 555                 560
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Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
                565                 570                 575

Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu
            580                 585                 590

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
        595                 600                 605

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
    610                 615                 620

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
625                 630                 635                 640

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
                645                 650                 655

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
            660                 665                 670

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
        675                 680                 685

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
    690                 695                 700

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
705                 710                 715                 720

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr
        755                 760                 765

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
    770                 775                 780

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
785                 790                 795                 800

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
                805                 810                 815

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
            820                 825                 830

Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val
        835                 840                 845

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
    850                 855                 860

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
865                 870                 875                 880

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
                885                 890                 895

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
            900                 905                 910

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
        915                 920                 925

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
    930                 935                 940

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
945                 950                 955                 960

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
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                965                 970                 975

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            980                 985                 990


<210> SEQ ID NO 17
<211> LENGTH: 692
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD0899

<400> SEQUENCE: 17

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

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

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

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly
225                 230                 235                 240

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro Met
                245                 250                 255

Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser
            260                 265                 270

Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr
        275                 280                 285

Cys Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His
    290                 295                 300

Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Ser Gly Gly Ser Gly Gly
305                 310                 315                 320

Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln Asn Trp
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               325                 330                 335

Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser
            340                 345                 350

Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser
        355                 360                 365

Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile
    370                 375                 380

Ser Cys Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu
385                 390                 395                 400

Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu
                405                 410                 415

Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu
            420                 425                 430

Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser
        435                 440                 445

Gly Gly Gly Gly Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
    450                 455                 460

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
465                 470                 475                 480

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                485                 490                 495

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
            500                 505                 510

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        515                 520                 525

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    530                 535                 540

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
545                 550                 555                 560

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                565                 570                 575

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
            580                 585                 590

Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
        595                 600                 605

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
    610                 615                 620

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
625                 630                 635                 640

Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
                645                 650                 655

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
            660                 665                 670

Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Ser Ser Asp Tyr Lys Asp
        675                 680                 685

Asp Asp Asp Lys
    690


<210> SEQ ID NO 18
<211> LENGTH: 697
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: QD0900

<400> SEQUENCE: 18

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
20 25 30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
35 40 45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
50 55 60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
100 105 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
115 120 125

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

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

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
165 170 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
180 185 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
195 200 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
210 215 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly
225 230 235 240

Gly Gly Gly Ser Gly Gly Gly Gly Asn Trp Val Asn Val Ile Ser Asp
245 250 255

Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr
260 265 270

Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met
275 280 285

Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Cys Glu Ser Gly Asp
290 295 300

Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn
305 310 315 320

Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys
325 330 335

Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val
340 345 350

His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly Ser Gly
355 360 365

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
370 375 380

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Gly Ser Gly Gly Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala
385                 390                 395                 400

Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile
                405                 410                 415

Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Cys Ser Leu Thr Glu
            420                 425                 430

Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser
        435                 440                 445

Leu Lys Cys Ile Arg Gly Gly Gly Gly Ser Glu Ser Lys Tyr Gly Pro
    450                 455                 460

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
465                 470                 475                 480

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                485                 490                 495

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
            500                 505                 510

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        515                 520                 525

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
    530                 535                 540

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
545                 550                 555                 560

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
                565                 570                 575

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            580                 585                 590

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala
        595                 600                 605

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    610                 615                 620

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
625                 630                 635                 640

Asp Gly Ser Phe Phe Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg
                645                 650                 655

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            660                 665                 670

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Ser
        675                 680                 685

Ser Asp Tyr Lys Asp Asp Asp Asp Lys
    690                 695


<210> SEQ ID NO 19
<211> LENGTH: 740
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD0901

<400> SEQUENCE: 19

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30
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Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

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

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

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly
225                 230                 235                 240

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Val Thr Gln Glu
                245                 250                 255

Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Arg
            260                 265                 270

Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln
        275                 280                 285

Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Asn Lys
    290                 295                 300

Arg Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly
305                 310                 315                 320

Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu
                325                 330                 335

Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Leu Trp Val Phe Gly Gly Gly
            340                 345                 350

Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        355                 360                 365

Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
    370                 375                 380

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
385                 390                 395                 400

Thr Phe Asn Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
                405                 410                 415

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
            420                 425                 430
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Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
        435                 440                 445

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
    450                 455                 460

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
465                 470                 475                 480

Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
                485                 490                 495

Ser Ser Gly Gly Gly Gly Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro
            500                 505                 510

Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
        515                 520                 525

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    530                 535                 540

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
545                 550                 555                 560

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                565                 570                 575

Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            580                 585                 590

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        595                 600                 605

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
    610                 615                 620

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
625                 630                 635                 640

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
                645                 650                 655

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            660                 665                 670

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        675                 680                 685

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
    690                 695                 700

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
705                 710                 715                 720

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Ser Ser His His
                725                 730                 735

His His His His
            740


<210> SEQ ID NO 20
<211> LENGTH: 731
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3667

<400> SEQUENCE: 20

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30
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Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
                165                 170                 175

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
        195                 200                 205

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
    210                 215                 220

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
            260                 265                 270

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Trp Val Asn Val Ile
        275                 280                 285

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
    290                 295                 300

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
305                 310                 315                 320

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Cys Glu Ser
                325                 330                 335

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
            340                 345                 350

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
        355                 360                 365

Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
    370                 375                 380

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
385                 390                 395                 400

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
                405                 410                 415

Gly Gly Gly Ser Gly Gly Ile Thr Cys Pro Pro Pro Met Ser Val Glu
            420                 425                 430

His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg
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        435                 440                 445

Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Cys Ser Leu
    450                 455                 460

Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr
465                 470                 475                 480

Pro Ser Leu Lys Cys Ile Arg Gly Gly Gly Gly Ser Glu Ser Lys Tyr
                485                 490                 495

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
            500                 505                 510

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        515                 520                 525

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
    530                 535                 540

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
545                 550                 555                 560

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
                565                 570                 575

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            580                 585                 590

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
        595                 600                 605

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    610                 615                 620

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
625                 630                 635                 640

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                645                 650                 655

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            660                 665                 670

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Arg Leu Thr Val Asp Lys
        675                 680                 685

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    690                 695                 700

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
705                 710                 715                 720

Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys
                725                 730


<210> SEQ ID NO 21
<211> LENGTH: 763
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD3668

<400> SEQUENCE: 21

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
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    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
                165                 170                 175

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
        195                 200                 205

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
    210                 215                 220

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
            260                 265                 270

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
        275                 280                 285

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
    290                 295                 300

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
305                 310                 315                 320

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
                325                 330                 335

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
            340                 345                 350

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
        355                 360                 365

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
    370                 375                 380

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
385                 390                 395                 400

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Val
                405                 410                 415

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
            420                 425                 430

Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn
        435                 440                 445

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
    450                 455                 460
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Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
465                 470                 475                 480

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
                485                 490                 495

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Leu Trp Val Phe
            500                 505                 510

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Glu Ser
        515                 520                 525

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
    530                 535                 540

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
545                 550                 555                 560

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
                565                 570                 575

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            580                 585                 590

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
        595                 600                 605

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
    610                 615                 620

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
625                 630                 635                 640

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
                645                 650                 655

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
            660                 665                 670

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
        675                 680                 685

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
    690                 695                 700

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
705                 710                 715                 720

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
                725                 730                 735

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
            740                 745                 750

Leu Gly Gly Ser Ser His His His His His His
        755                 760


<210> SEQ ID NO 22
<211> LENGTH: 725
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD0902

<400> SEQUENCE: 22

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45
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Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
                165                 170                 175

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
        195                 200                 205

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
    210                 215                 220

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
            260                 265                 270

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro
        275                 280                 285

Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr
    290                 295                 300

Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly
305                 310                 315                 320

Thr Cys Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala
                325                 330                 335

His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Ser Gly Gly Ser Gly
            340                 345                 350

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln Asn
        355                 360                 365

Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln
    370                 375                 380

Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro
385                 390                 395                 400

Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val
                405                 410                 415

Ile Ser Cys Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn
            420                 425                 430

Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr
        435                 440                 445
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Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys
    450                 455                 460

Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr
465                 470                 475                 480

Ser Gly Gly Gly Gly Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
                485                 490                 495

Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
            500                 505                 510

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        515                 520                 525

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
    530                 535                 540

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
545                 550                 555                 560

Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                565                 570                 575

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            580                 585                 590

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
        595                 600                 605

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
    610                 615                 620

Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe
625                 630                 635                 640

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                645                 650                 655

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            660                 665                 670

Phe Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
        675                 680                 685

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    690                 695                 700

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Ser Ser Asp Tyr Lys
705                 710                 715                 720

Asp Asp Asp Asp Lys
                725


<210> SEQ ID NO 23
<211> LENGTH: 763
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD0903

<400> SEQUENCE: 23

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
    50                  55                  60
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Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
                165                 170                 175

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
        195                 200                 205

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
    210                 215                 220

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
            260                 265                 270

Glu Leu Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
        275                 280                 285

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
    290                 295                 300

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
305                 310                 315                 320

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
                325                 330                 335

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
            340                 345                 350

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
        355                 360                 365

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
    370                 375                 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
385                 390                 395                 400

Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu
                405                 410                 415

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
            420                 425                 430

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
        435                 440                 445

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
    450                 455                 460

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
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465                 470                 475                 480

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
                485                 490                 495

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
            500                 505                 510

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu Ser
        515                 520                 525

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
    530                 535                 540

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
545                 550                 555                 560

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
                565                 570                 575

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            580                 585                 590

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
        595                 600                 605

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
    610                 615                 620

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
625                 630                 635                 640

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
                645                 650                 655

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
            660                 665                 670

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
        675                 680                 685

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
    690                 695                 700

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
705                 710                 715                 720

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
                725                 730                 735

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
            740                 745                 750

Leu Gly Gly Ser Ser His His His His His His
        755                 760


<210> SEQ ID NO 24
<211> LENGTH: 731
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD0904

<400> SEQUENCE: 24

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
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    50                  55                  60

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
                85                  90                  95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln
145                 150                 155                 160

Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn
                165                 170                 175

Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr
            180                 185                 190

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205

Tyr Gly Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
225                 230                 235                 240

Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn Asp His Ser Tyr Pro Phe
                245                 250                 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            260                 265                 270

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Trp Val Asn Val Ile
        275                 280                 285

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
    290                 295                 300

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
305                 310                 315                 320

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Cys Glu Ser
                325                 330                 335

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
            340                 345                 350

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
        355                 360                 365

Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
    370                 375                 380

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
385                 390                 395                 400

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
                405                 410                 415

Gly Gly Gly Ser Gly Gly Ile Thr Cys Pro Pro Pro Met Ser Val Glu
            420                 425                 430

His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg
        435                 440                 445

Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Cys Ser Leu
    450                 455                 460
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Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr
465                 470                 475                 480

Pro Ser Leu Lys Cys Ile Arg Gly Gly Gly Gly Ser Glu Ser Lys Tyr
                485                 490                 495

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
            500                 505                 510

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        515                 520                 525

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
    530                 535                 540

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
545                 550                 555                 560

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
                565                 570                 575

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            580                 585                 590

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
        595                 600                 605

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    610                 615                 620

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
625                 630                 635                 640

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                645                 650                 655

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            660                 665                 670

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Arg Leu Thr Val Asp Lys
        675                 680                 685

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    690                 695                 700

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
705                 710                 715                 720

Gly Ser Ser Asp Tyr Lys Asp Asp Asp Asp Lys
                725                 730


<210> SEQ ID NO 25
<211> LENGTH: 763
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD0905

<400> SEQUENCE: 25

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65                  70                  75                  80
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Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
                85                  90                  95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln
145                 150                 155                 160

Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn
                165                 170                 175

Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr
            180                 185                 190

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205

Tyr Gly Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
225                 230                 235                 240

Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn Asp His Ser Tyr Pro Phe
                245                 250                 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            260                 265                 270

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
        275                 280                 285

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
    290                 295                 300

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
305                 310                 315                 320

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
                325                 330                 335

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
            340                 345                 350

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
        355                 360                 365

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
    370                 375                 380

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
385                 390                 395                 400

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Val
                405                 410                 415

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
            420                 425                 430

Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn
        435                 440                 445

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
    450                 455                 460

Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
465                 470                 475                 480
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Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
                485                 490                 495

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Leu Trp Val Phe
            500                 505                 510

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser Glu Ser
        515                 520                 525

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
    530                 535                 540

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
545                 550                 555                 560

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
                565                 570                 575

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            580                 585                 590

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
        595                 600                 605

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
    610                 615                 620

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
625                 630                 635                 640

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
                645                 650                 655

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
            660                 665                 670

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
        675                 680                 685

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
    690                 695                 700

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
705                 710                 715                 720

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
                725                 730                 735

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
            740                 745                 750

Leu Gly Gly Ser Ser His His His His His His
        755                 760


<210> SEQ ID NO 26
<211> LENGTH: 725
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD0906

<400> SEQUENCE: 26

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60
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Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
                85                  90                  95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln
145                 150                 155                 160

Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn
                165                 170                 175

Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr
            180                 185                 190

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205

Tyr Gly Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
225                 230                 235                 240

Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn Asp His Ser Tyr Pro Phe
                245                 250                 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            260                 265                 270

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ile Thr Cys Pro Pro Pro
        275                 280                 285

Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr
    290                 295                 300

Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly
305                 310                 315                 320

Thr Cys Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala
                325                 330                 335

His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg Ser Gly Gly Ser Gly
            340                 345                 350

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu Gln Asn
        355                 360                 365

Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln
    370                 375                 380

Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro
385                 390                 395                 400

Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val
                405                 410                 415

Ile Ser Cys Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn
            420                 425                 430

Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr
        435                 440                 445

Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys
    450                 455                 460

Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn Thr
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465                 470                 475                 480

Ser Gly Gly Gly Gly Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
                485                 490                 495

Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
            500                 505                 510

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        515                 520                 525

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
    530                 535                 540

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
545                 550                 555                 560

Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                565                 570                 575

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            580                 585                 590

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
        595                 600                 605

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
    610                 615                 620

Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe
625                 630                 635                 640

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                645                 650                 655

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            660                 665                 670

Phe Leu Val Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
        675                 680                 685

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    690                 695                 700

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Ser Ser Asp Tyr Lys
705                 710                 715                 720

Asp Asp Asp Asp Lys
                725


<210> SEQ ID NO 27
<211> LENGTH: 763
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD0907

<400> SEQUENCE: 27

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65                  70                  75                  80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
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-continued

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                85                  90                  95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln
145                 150                 155                 160

Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn
                165                 170                 175

Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr
            180                 185                 190

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        195                 200                 205

Tyr Gly Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
225                 230                 235                 240

Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn Asp His Ser Tyr Pro Phe
                245                 250                 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            260                 265                 270

Glu Leu Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
        275                 280                 285

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
    290                 295                 300

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
305                 310                 315                 320

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
                325                 330                 335

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
            340                 345                 350

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
        355                 360                 365

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
    370                 375                 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
385                 390                 395                 400

Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu
                405                 410                 415

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp
            420                 425                 430

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
        435                 440                 445

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
    450                 455                 460

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
465                 470                 475                 480

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
                485                 490                 495
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His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly
            500                 505                 510

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu Ser
        515                 520                 525

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
    530                 535                 540

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
545                 550                 555                 560

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
                565                 570                 575

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            580                 585                 590

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
        595                 600                 605

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
    610                 615                 620

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
625                 630                 635                 640

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
                645                 650                 655

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
            660                 665                 670

Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
        675                 680                 685

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
    690                 695                 700

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
705                 710                 715                 720

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
                725                 730                 735

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
            740                 745                 750

Leu Gly Gly Ser Ser His His His His His His
        755                 760


<210> SEQ ID NO 28
<211> LENGTH: 721
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: QD0728

<400> SEQUENCE: 28

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                   10                  15

Val Gln Cys Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg Glu
65                  70                  75                  80
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-continued

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Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Gln Asn Asp His Ser Tyr Pro Phe Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
145                 150                 155                 160

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
                165                 170                 175

Thr Ser Tyr Ile Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
            180                 185                 190

Glu Trp Met Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
        195                 200                 205

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
    210                 215                 220

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Arg Leu Gly Phe Thr Thr Arg Asn Ala Met Asp Tyr
                245                 250                 255

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
            260                 265                 270

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Trp Val Asn Val Ile
        275                 280                 285

Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp
    290                 295                 300

Ala Thr Leu Tyr Thr Glu Ser Asp Val His Pro Ser Cys Lys Val Thr
305                 310                 315                 320

Ala Met Lys Cys Phe Leu Leu Glu Leu Gln Val Ile Ser Cys Glu Ser
                325                 330                 335

Gly Asp Ala Ser Ile His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala
            340                 345                 350

Asn Asn Ser Leu Ser Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys
        355                 360                 365

Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser
    370                 375                 380

Phe Val His Ile Val Gln Met Phe Ile Asn Thr Ser Ser Gly Gly Gly
385                 390                 395                 400

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
                405                 410                 415

Gly Gly Gly Ser Gly Gly Ile Thr Cys Pro Pro Pro Met Ser Val Glu
            420                 425                 430

His Ala Asp Ile Trp Val Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg
        435                 440                 445

Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys Ala Gly Thr Cys Ser Leu
    450                 455                 460

Thr Glu Cys Val Leu Asn Lys Ala Thr Asn Val Ala His Trp Thr Thr
465                 470                 475                 480
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-continued

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Pro Ser Leu Lys Cys Ile Arg Gly Gly Gly Gly Ser Glu Ser Lys Tyr
                485                 490                 495

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
            500                 505                 510

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        515                 520                 525

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
    530                 535                 540

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
545                 550                 555                 560

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
                565                 570                 575

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            580                 585                 590

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
        595                 600                 605

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    610                 615                 620

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
625                 630                 635                 640

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                645                 650                 655

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            660                 665                 670

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
        675                 680                 685

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    690                 695                 700

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
705                 710                 715                 720

Lys
```

<210> SEQ ID NO 29
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VHCDR1

<400> SEQUENCE: 29

```
Thr Tyr Ala Met Asn
1               5
```

<210> SEQ ID NO 30
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VHCDR2

<400> SEQUENCE: 30

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

Val Lys Asp
```

-continued

<210> SEQ ID NO 31
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VHCDR3

<400> SEQUENCE: 31

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

<210> SEQ ID NO 32
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VLCDR1

<400> SEQUENCE: 32

Arg Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala
1 5 10

<210> SEQ ID NO 33
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VLCDR2

<400> SEQUENCE: 33

Gly Thr Asn Lys Arg Ala Pro
1 5

<210> SEQ ID NO 34
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VLCDR3

<400> SEQUENCE: 34

Ala Leu Trp Tyr Ser Asn Leu Trp Val
1 5

<210> SEQ ID NO 35
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VHCDR2

<400> SEQUENCE: 35

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

Val Lys Asp

<210> SEQ ID NO 36
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VHCDR3

<400> SEQUENCE: 36

-continued

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

<210> SEQ ID NO 37
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VLCDR2

<400> SEQUENCE: 37

Gly Thr Asn Leu Arg Ala Pro
1 5

<210> SEQ ID NO 38
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VLCDR2

<400> SEQUENCE: 38

Gly Thr Trp Leu Arg Ala Pro
1 5

<210> SEQ ID NO 39
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VLCDR3

<400> SEQUENCE: 39

Ala Leu Trp Arg Ser Gly Gly Trp Val
1 5

<210> SEQ ID NO 40
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VLCDR3

<400> SEQUENCE: 40

Ala Leu Trp Asn Lys Gly Gly Trp Val
1 5

<210> SEQ ID NO 41
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VLCDR3

<400> SEQUENCE: 41

Ala Leu Trp Asn Ser Gly Gly Trp Val
1 5

<210> SEQ ID NO 42
<211> LENGTH: 205
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IL-15~IL-15Ra

-continued

<400> SEQUENCE: 42

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Cys Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ile Thr Cys Pro
130 135 140

Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val Lys Ser Tyr Ser
145 150 155 160

Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly Phe Lys Arg Lys
165 170 175

Ala Gly Thr Cys Ser Leu Thr Glu Cys Val Leu Asn Lys Ala Thr Asn
180 185 190

Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile Arg
195 200 205

<210> SEQ ID NO 43
<211> LENGTH: 199
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IL-15~IL-15Ra

<400> SEQUENCE: 43

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1 5 10 15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
20 25 30

Phe Lys Arg Lys Ala Gly Thr Cys Ser Leu Thr Glu Cys Val Leu Asn
35 40 45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Ser Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly
65 70 75 80

Gly Gly Ser Leu Gln Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys
85 90 95

Ile Glu Asp Leu Ile Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr
100 105 110

Glu Ser Asp Val His Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe
115 120 125

Leu Leu Glu Leu Gln Val Ile Ser Cys Glu Ser Gly Asp Ala Ser Ile

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    130                 135                 140

His Asp Thr Val Glu Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser
145                 150                 155                 160

Ser Asn Gly Asn Val Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu
                165                 170                 175

Glu Glu Lys Asn Ile Lys Glu Phe Leu Gln Ser Phe Val His Ile Val
            180                 185                 190

Gln Met Phe Ile Asn Thr Ser
        195


<210> SEQ ID NO 44
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IL-15

<400> SEQUENCE: 44

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1               5                   10                  15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
            20                  25                  30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
        35                  40                  45

Val Ile Ser Cys Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
    50                  55                  60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65                  70                  75                  80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
                85                  90                  95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
            100                 105                 110

Thr Ser Ser
        115


<210> SEQ ID NO 45
<211> LENGTH: 65
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IL-15Ra

<400> SEQUENCE: 45

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Cys Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg
65
```

1-32. (canceled)

33. An anti-CD3 antibody variant, comprising a heavy chain variable region and a light chain variable region; the heavy chain variable region comprises: VHCDR1, VHCDR2, and VHCDR3; the light chain variable region comprises: VLCDR1, VLCDR2, and VLCDR3; the amino acid sequence of the anti-CD3 antibody comprises VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 shown in SEQ ID NO: 29-34; wherein:

the mutation site of the anti-CD3 antibody variant comprises any one or more of the following sites:

position 10 in SEQ ID NO: 30,

positions 2 and 7 in SEQ ID NO: 31,

positions 3 and 4 in SEQ ID NO: 33,

positions 4, 5, 6, and 7 in SEQ ID NO: 34;

preferably, the mutation refers to amino acid substitution.

34. The anti-CD3 antibody variant of claim **33**, wherein the mutation site of the variant comprises any one or more of the following sites:

A in position 10 substituted with E in the sequence of SEQ ID NO: 30,

G in position 2 substituted with S, and S in position 7 substituted with G in the sequence of SEQ ID NO: 31,

N in position 3 substituted with W, and K in position 4 substituted with L in the sequence of SEQ ID NO: 33,

Y in position 4 substituted with N or R, S in position 5 substituted with K, N in position 6 substituted with G, and L in position 7 substituted with G in the sequence of SEQ ID NO: 34.

35. The anti-CD3 antibody variant of claim **33**, wherein

the amino acid sequence of VHCDR2 is shown in SEQ ID NO: 35; or

the amino acid sequence of VHCDR3 is shown in SEQ ID NO: 36; or

the amino acid sequence of VLCDR2 is shown in SEQ ID NO: 37 or 38; or

the amino acid sequence of VLCDR3 is shown in SEQ ID NO: 39, 40 or 41.

36. The anti-CD3 antibody variant of claim **33**, wherein the amino acid sequences of VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 are shown in any one of the following groups of sequences:

(1) SEQ ID NOs: 29, 35, 31, 32, 37, 39;

(2) SEQ ID NOs: 29, 35, 36, 32, 37, 40;

(3) SEQ ID NOs: 29, 35, 36, 32, 38, 41.

37. The anti-CD3 antibody variant of claim **33**, wherein the heavy chain variable region and/or light chain variable region of the antibody variant are selected from the heavy chain variable region and/or light chain variable region has the sequence shown in or have at least 90% sequence identity with SEQ ID NO: 1, 2, or 3.

38. The anti-CD3 antibody variant of claim **33**, wherein there is a mutation used to form a disulfide bond between the heavy chain variable region and the light chain variable region, wherein the mutation site comprises any one or more of the following combination forms, according to EU numbering, and the heavy chain variable region is represented by VH, while the light chain variable region is represented by VL:

	Disulfide bond mutation site	
	VH	VL
Combination 1	37C	95C
Combination 2	44C	100C
Combination 3	44C	105C
Combination 4	45C	87C
Combination 5	100C	50C
Combination 6	100bC	49C
Combination 7	98C	46C
Combination 8	101C	46C
Combination 9	105C	43C
Combination 10	106C	57C

39. The anti-CD3 antibody variant of claim **33**, wherein the variant further comprises: a heavy chain constant region selected from human IgG1, IgG2, IgG3, or IgG4 or a variant thereof; and a light chain constant region selected from human κ, λ or a variant thereof; wherein the heavy chain constant region comprises: an Fc fragment or a variant thereof.

40. The anti-CD3 antibody variant of claim **33**, wherein the antibody variant is a scFv, which comprises a heavy chain variable region, a light chain variable region, and a linker connecting the heavy chain variable region and the light chain variable region, wherein the amino acid sequence of the linker is preferably several GGGGS replicates, more preferably three GGGGS replicates.

41. A method for inhibiting or treating cancer, comprising administering the anti-CD3 antibody variant of claim **33** to a subject in need;

wherein the cancer is selected from the following cancers or occurs in the following areas: colorectal, breast, ovary, pancreas, stomach, prostate, kidney, cervix, bone marrow cancer, lymphatic cancer, leukemia, thyroid, endometrium, uterus, bladder, neuroendocrine, head and neck, liver, nasopharyngeal, testicle, small cell lung cancer, non-small cell lung cancer, melanoma, basal cell skin cancer, squamous cell skin cancer, dermatofibrosarcoma protuberans, Merkel cell carcinoma, glioblastoma, glioma, sarcoma, mesothelioma, and myelodysplastic syndrome.

42. A nucleic acid molecule, which encodes the anti-CD3 antibody variant of claim **33**.

43. An anti-tumor associated antigen (TAA)/anti-CD3 protein molecule, wherein the molecule is in a form of heterodimer, comprising a first monomer and a second monomer;

the first monomer comprises: (a) an Fd fragment; (b) a light chain fragment and a first Fc chain;

the second monomer comprises: (a) an Fd fragment; (b) a light chain fragment, an anti-CD3 antibody fragment, and a second Fc chain;

the light chain fragment comprises a VL domain and a CL domain; the Fd fragment comprises a VH domain and a CH1 domain; in the first monomer or the second monomer, the light chain fragment pairs with the Fd fragment to form an anti-TAA Fab domain; wherein the light chain fragment of the first monomer is fused with the first Fc chain; the N-terminus of the anti-CD3 antibody fragment is fused with the light chain fragment of the second monomer, and the C-terminus is fused with the second Fc chain;

or

the first monomer comprises: (a) an Fd fragment; (b) a light chain fragment, a cytokine functional region, and a first Fc chain;

the second monomer comprises: (a) an Fd fragment; (b) a light chain fragment, an anti-CD3 antibody fragment, and a second Fc chain;

the cytokine functional region comprises IL-15 and IL-15Ra; wherein the N-terminus of the cytokine functional region is fused with the light chain fragment of the first monomer, and the C-terminus is fused with the first Fc chain; the N-terminus of the anti-CD3 antibody fragment is fused with the light chain fragment of the second monomer, and the C-terminus is fused with the second Fc chain;

or

the first monomer comprises: an anti-TAA antibody fragment, a cytokine functional region, and a first Fc chain;

the second monomer comprises: an anti-TAA antibody fragment, an anti-CD3 antibody fragment, and a second Fc chain; wherein,

the N-terminus of the cytokine functional region is fused with the anti-TAA antibody fragment of the first monomer, and the C-terminus is fused with the first Fc chain; The N-terminus of the anti-CD3 antibody fragment is fused with the anti-TAA antibody fragment of the second monomer, and the C-terminus is fused with the second Fc chain;

the first Fc chain and the second Fc chain are interchangeable;

preferably, the amino acid sequence of the anti-CD3 antibody fragment is selected from an antibody, an antibody fragment, a single domain antibody, or a humanized form thereof that specifically binds to CD3; preferably, the amino acid sequence of the anti-CD3 antibody fragment is selected from SP34, OKT3, UCTH1 or a derivative thereof.

44. The anti-tumor associated antigen (TAA)/anti-CD3 protein molecule of claim **43**, wherein

the anti-TAA antibody fragment is in the form of scFv, comprising: a heavy chain variable region (VH), a light chain variable region (VL), and a linker connecting the heavy chain variable region and the light chain variable region; from the N-terminus to the C-terminus of the peptide chain, the fusion order of amino acids of the anti-TAA antibody fragment is "VH~VL", or "VL~VH"; wherein "~" represents a linker; or

the anti-CD3 antibody fragment is in the form of scFv, comprising: a heavy chain variable region (VH), a light chain variable region (VL), and a linker connecting the heavy chain variable region and the light chain variable region; from the N-terminus to the C-terminus of the peptide chain, the fusion order of the amino acids of the anti-CD3 antibody fragment is "VH~VL", or "VL~VH"; wherein "~" represents a linker; or

from the N-terminus to the C-terminus of the peptide chain, the fusion order of the amino acid fragments of the cytokine functional region is "IL-15~IL-15Ra", or "IL-15Ra~IL-15"; wherein "~" represents a linker; preferably, the sequence of IL-15~IL-15Ra is shown in SEQ ID NO: 42, and the sequence of IL-15Ra~IL-15 is shown in SEQ ID NO: 43.

45. The anti-tumor associated antigen (TAA)/anti-CD3 protein molecule of claim **43**, wherein the anti-CD3 antibody fragment comprises a heavy chain variable region and a light chain variable region; the heavy chain variable region of the anti-CD3 antibody fragment comprises: VHCDR1, VHCDR2, and VHCDR3; the light chain variable region of the anti-CD3 antibody fragment comprises: VLCDR1, VLCDR2, VLCDR3; the amino acid sequences of VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, and VLCDR3 are shown in any group of the following: (1) SEQ ID NO: 29, 35, 31, 32, 37, 39; (2) SEQ ID NO: 29, 35, 36, 32, 37, 40; (3) SEQ ID NO: 29, 35, 36, 32, 38, 41.

46. The anti-tumor associated antigen (TAA)/anti-CD3 protein molecule of claim **43**, wherein the IL-15Ra and IL-15 form an IL-15/IL-15Ra complex; IL-15 comprises: IL-15 and mutations, truncations, and various derivants thereof that can bind to IL-15Ra; IL-15Ra comprises: IL-15Ra and mutations, truncations, and various derivatives thereof that can bind to IL-15; wherein the IL-15 comprises but is not limited to any one of the mutation modes shown in the following combinations, and the numbering method is to start counting from the first amino acid in the amino acid sequence of the IL-15 as the first position; preferably, the maternal sequence of IL-15 is shown in SEQ ID NO: 44;

Combination	IL15 mutation
1	N1D
2	N4D
3	D8N
4	D30N
5	D61N
6	E64Q
7	N65D
8	Q108E
9	N1D/D61N
10	N1D/E64Q
11	N4D/D61N
12	N4D/E64Q
13	D8N/D61N
14	D8N/E64Q
15	D61N/E64Q
16	E64Q/Q108E
17	N1D/N4D/D8N
18	D61N/E64Q/N65D
19	N1D/D61N/E64Q/Q108E
20	N4D/D61N/E64Q/Q108E

preferably, the IL-15/IL-15Ra complex includes but not limited to any one of the mutation modes shown in the following combinations, and the numbering method is to start counting from the first amino acid in the amino acid sequence of IL-15 or IL-15Ra as the first position; preferably, the maternal sequence of IL-15 is shown in SEQ ID NO: 44; the maternal sequence of the IL-15Ra is shown in SEQ ID NO: 45:

Combination	IL15	IL5Ra
1	wt	D96
2	wt	D96/P97
3	wt	D96/P97/A98
4	E87C	D96/C97
5	E87C	D96/P97/C98
6	E87C	D96/C97/A98
7	V49C	S40C
8	L52C	S40C
9	E89C	K34C
10	Q48C	G38C
11	E53C	L42C

-continued

Combination	IL15	IL5Ra
12	C42S	A37C
13	L45C	G38C
14	L45C	A37C

47. The anti-tumor associated antigen (TAA)/anti-CD3 protein molecule of claim **43**, wherein the TAA is selected from: CD20, CD19, CD30, CD33, CD38, CD40, CD52, slamf7, GD2, CD24, CD47, CD133, CD239, CD276, PD-1, CEA, Epcam, Trop2, TAG72, MUC1, MUC16, mesothelin, folr1, CLDN18.2, PDL1, EGFR, EGFR VIII, C-MET, HER2, FGFR2, FGFR3, PSMA, PSCA, EphA2, ADAM17, 17-A1, NKG2D ligands, MCSP, LGR5, SSEA3, SLC34A2, BCMA, GPNMB or Glypican-3.

48. The anti-tumor associated antigen (TAA)/anti-CD3 protein molecule of claim **43**, wherein the first Fc chain and the second Fc chain are polymerized to form an Fc fragment; the Fc fragment is selected from human IgG1 Fc, human IgG2 Fc, human IgG3 Fc, human IgG4 Fc or a variant thereof, preferably from IgG1 Fc, or human IgG4 Fc or a variant thereof; the protein molecule is in a form of Fc heterodimer; preferably, the Fc heterodimer includes but is not limited to a combination of the following mutations, according to EU numbering:

Combination	FC	Heterodimer mutation (EU numbering)
1	first FC chain	T366Y
	second FC chain	Y407T
2	first FC chain	T366W
	second FC chain	T366S/L368A/Y407V
3	first FC chain	S354C/T366W
	second FC chain	Y349C/T366S/L368A/Y407V
4	first FC chain	S364H/F405A
	second FC chain	Y349T/T394F
5	first FC chain	T350V/L351Y/F405A/Y407V
	second FC chain	T350V/T366L/K392L/T394W
6	first FC chain	K392D/K409D
	second FC chain	E356K/D399K
7	first FC chain	D221EP228E/L368E
	second FC chain	D221R/P228R/K409R
8	first FC chain	K360EK409W
	second FC chain	Q347R/D399V/F405T
9	first FC chain	K360E/K409W/Y349C
	second FC chain	Q347R/D399V/F405T/S354C
10	first FC chain	K370E/K409W
	second FC chain	E357ND399VF405T

-continued

Combination	FC	Heterodimer mutation (EU numbering)
11	first FC chain	F405L
	second FC chain	K409R
12	first FC chain	K360D/D399M/Y407A
	second FC chain	E345R/Q347R/T366V/K409V
13	first FC chain	Y349S/K370Y/T366M/K409V
	second FC chain	E356G/E357D/S364Q/Y407A
14	first FC chain	L351D/L368E
	second FC chain	L351K/T366K
15	first FC chain	GQPFRPEVHLIPPSREMTKNQVSLTCLARGFYPKDAVEWESNGQPENNYKTTPSRQEPSQGTTTFAVTSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKTEL
	second FC chain	GQPREPQVYTPPPSEEAINELVILTCLVKGFYPSDAVEWLQGSQELPREKYLTWAPVLDSDGSFFLYSLRVAAEDWKKGDTFSCSVMHEALHNHYTQKSDR
16	first FC chain	L368D/K370S
	second FC chain	E357Q/S364K
17	first FC chain	S354C/T366W/K409A
	second FC chain	Y349C/T366S/L368A/Y407V/F405K
18	first FC chain	S354C/T366W/F405K/K360E/Q347E
	second FC chain	Y349C/T366S/L368A/Y407V/Q347R/T394W
19	first FC chain	T366W/K409A
	second FC chain	T366S/L368G/Y407A/F405K
20	first FC chain	knobs (T366W/F405K)
	second FC chain	holes (T366S/L368G/Y407A/K409A)
21	first FC chain	Q347A/S364K/T366VK370T/K392YF405S/Y407V/K409W/T411N
	second FC chain	Q347E/Y349AL351F/S364T/T366V//K370T/T394D/V397L/D399E/D401Q/F405A/Y407S/K409R/T411R

-continued

Combination	FC	Heterodimer mutation (EU numbering)
22	first FC chain	K274Q/N276K/ Y300F/A339T/ Q347A/S364K/ T366V/K370T/ N384S /K392Y/V397M /F405S/Y407V /K409W/T411N /V4221/H435R/ Y436F
	second FC chain	Q347E/Y349A/ L351F/S364T/ T366V/K370T/ T394D/V397L/ D399E/D401Q/ F405A/Y407S/ K409R/T411R

49. The anti-tumor associated antigen (TAA)/anti-CD3 protein molecule of claim **43**, wherein the protein molecule comprises an Fc fragment that selectively eliminates immune effector functions, including but not limited to a combination of the following mutations, according to EU numbering:

IgG	FC Mutate(EU numbing)
IgG1	L234A, L235A
	L234A, L235A, P329G
	L234F, L235E, P331S
	D265A, N297A
	L234F, L235E, N297A
	L234F, L235E, D265A
	L234A, L235E, P331S
	L234A, L235E, N297A
	L234A, L235E, D265A
	L234A, L235A, P331S
	L234A, L235A, N297A
	L234A, L235A, D265A
	L235E, D265A, P331S
	L235E, N297A, P331S
	L235E, N297A
	L235A, D265A, P331S
	L235A, N297A, P331S
	N297Q
	N297A
	N297G
	A287C, N297G, L306C
	R292C, N297G, V302C
hIgG4	S228P, L235E, P329G
	S228P, L235E
	S228P, F234A, L235E
	S228P, F234A, L235A
IgG2m4	ASTKGPSVFPLAPCSRSTS
	ESTAALGCLVKDYFPEPVTV
	SWNSGALTSGVHTFPAVLQS
	SGLYSLSSVVTVPSSNFGTQ
	TYTCNVDHKPSNTKVDKTVE
	RKCCVECPPCPAPPVAGPSV
	FLFPPKPKDTLMISRTPEVT
	CVVVDVSQEDPEVQFNWYVD
	GVEVHNAKTKPREEQFNSTY
	RVVSVLTVLHQDWLNGKEYK
	CKVSNKGLPSSIEKTISKAK
	GQPREPQVYTLPPSQEEMTK
	NQVSLTCLVKGFYPSDIAVE

-continued

IgG	FC Mutate(EU numbing)
	WESNGQPENNYKTTPPVLDS
	DGSFFLYSRLTVDKSRWQEG
	NVFSCSVMHEALHNHYTQKS
	LSLSLGK
	N297A
	N297Q
	N297G

50. The anti-tumor associated antigen (TAA)/anti-CD3 protein molecule of claim **43**, which is obtained by fusing amino acid fragments shown in any one of the following groups of sequences:

(1) SEQ ID NO:05, SEQ ID NO:06, SEQ ID NO:07;
(2) SEQ ID NO:08, SEQ ID NO:06, SEQ ID NO:07;
(3) SEQ ID NO:09, SEQ ID NO:06, SEQ ID NO:07;
(4) SEQ ID NO:10, SEQ ID NO:06, SEQ ID NO:07;
(5) SEQ ID NO:05, SEQ ID NO:17, SEQ ID NO:07;
(6) SEQ ID NO:01, SEQ ID NO:18, SEQ ID NO:07;
(7) SEQ ID NO: 19, SEQ ID NO: 17, SEQ ID NO:07;
(8) SEQ ID NO:19, SEQ ID NO:18, SEQ ID NO:07;
(9) SEQ ID NO:20, SEQ ID NO:21;
(10) SEQ ID NO:22, SEQ ID NO:21;
(11) SEQ ID NO:20, SEQ ID NO:23;
(12) SEQ ID NO:22, SEQ ID NO:23;
(13) SEQ ID NO:24, SEQ ID NO:25;
(14) SEQ ID NO:26, SEQ ID NO:25;
(15) SEQ ID NO:24, SEQ ID NO:27;
(16) SEQ ID NO:26, SEQ ID NO:27.

51. A nucleic acid molecule, which encodes the anti-tumor associated antigen (TAA)/anti-CD3 protein molecule of claim **43**.

52. A method for inhibiting or treating cancer, comprising administering the anti-tumor associated antigen (TAA)/anti-CD3 protein molecule of claim **43** to a subject in need, wherein the cancer is selected from the following cancers or occurs in the following areas: colorectal, breast, ovary, pancreas, stomach, prostate, kidney, cervix, bone marrow cancer, lymphatic cancer, leukemia, thyroid, endometrium, uterus, bladder, neuroendocrine, head and neck, liver, nasopharyngeal, testicle, small cell lung cancer, non-small cell lung cancer, melanoma, basal cell skin cancer, squamous cell skin cancer, dermatofibrosarcoma protuberans, Merkel cell carcinoma, glioblastoma, glioma, sarcoma, mesothelioma, and myelodysplastic syndrome.

53. An anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein, which comprises two polypeptide chains, any one of which comprises: an anti-TAA antibody fragment, a cytokine functional region, and an Fc fragment; the anti-TAA antibody fragment is in the form of scFv; the cytokine functional region comprises IL-15 and IL-15Ra; the N-terminus of the cytokine functional region is fused with the anti-TAA antibody fragment, and the C-terminus is fused with the Fc fragment.

54. The anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein of claim **53**, wherein the IL-15Ra and IL-15 form an IL-15/IL-15Ra complex; the IL-15 comprises: IL-15 and mutations, truncations, and various derivatives thereof that can bind to IL-15Ra; the IL-15Ra comprises: IL-15Ra and mutations, truncations, and various derivatives thereof that can bind to IL-15; wherein the IL-15 includes but is not limited to any one of

the mutation modes shown in the following combinations, and the numbering method is to start counting from the first amino acid in the amino acid sequence of IL-15 as the first position; preferably, the maternal sequence of IL-15 is shown in SEQ ID NO: 44:

Combination	IL15 mutation
1	N1D
2	N4D
3	D8N
4	D30N
5	D61N
6	E64Q
7	N65D
8	Q108E
9	N1D/D61N
10	N1D/E64Q
11	N4D/D61N
12	N4D/E64Q
13	D8N/D61N
14	D8N/E64Q
15	D61N/E64Q
16	E64Q/Q108E
17	N1D/N4D/D8N
18	D61N/E64Q/N65D
19	N1D/D61N/E64Q/Q108E
20	N4D/D61N/E64Q/Q108E

preferably, the IL-15/IL-15Ra complex includes but is not limited to any one of the mutation modes shown in the following combinations, and the numbering method is to start counting from the first amino acid in the amino acid sequence of IL-15 or IL-15Ra as the first position; preferably, the maternal sequence of IL-15 is shown in SEQ ID NO: 44; the maternal sequence of the IL-15Ra is shown in SEQ ID NO: 45:

Combination	IL15	IL5Ra
1	wt	D96
2	wt	D96/P97
3	wt	D96/P97/A98
4	E87C	D96/C97
5	E87C	D96/P97/C98
6	E87C	D96/C97/A98
7	V49C	S40C
8	L52C	S40C
9	E89C	K34C
10	Q48C	G38C
11	E53C	L42C
12	C42S	A37C
13	L45C	G38C
14	L45C	A37C

55. The anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein of claim **53**, wherein any polypeptide chain of the fusion protein has an amino acid sequence shown in SEQ ID NO: 28, or has at least 90% sequence identity with it.

56. A nucleic acid molecule, which encodes the anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein of claim **53**.

57. A method for inhibiting or treating cancer, comprising administering the anti-tumor associated antigen (TAA) and IL-15/IL-15Ra-containing fusion protein of claim **53** to a subject in need, wherein the cancer is selected from the following cancers or occurs in the following areas: colorectal, breast, ovary, pancreas, stomach, prostate, kidney, cervix, bone marrow cancer, lymphatic cancer, leukemia, thyroid, endometrium, uterus, bladder, neuroendocrine, head and neck, liver, nasopharyngeal, testicle, small cell lung cancer, non-small cell lung cancer, melanoma, basal cell skin cancer, squamous cell skin cancer, dermatofibrosarcoma protuberans, Merkel cell carcinoma, glioblastoma, glioma, sarcoma, mesothelioma, and myelodysplastic syndrome.

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