US012391743B2

(12) **United States Patent**
Zwaagstra et al.

(10) **Patent No.: US 12,391,743 B2**
(45) **Date of Patent: Aug. 19, 2025**

(54) **TGF-β-RECEPTOR ECTODOMAIN FUSION MOLECULES AND USES THEREOF**

(71) Applicant: **National Research Council of Canada**, Ottawa (CA)

(72) Inventors: **John C. Zwaagstra**, Laval (CA); **Traian Sulea**, Kirkland (CA); **Maria L. Jaramillo**, Beaconsfield (CA); **Maureen D. O'Connor**, Beaconsfield (CA); **Anne E. G. Lenferink**, Lorraine (CA)

(73) Assignee: **National Research Council of Canada**, Ottawa (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 113 days.

(21) Appl. No.: **17/523,602**

(22) Filed: **Nov. 10, 2021**

(65) **Prior Publication Data**

US 2022/0169702 A1 Jun. 2, 2022

Related U.S. Application Data

(63) Continuation of application No. 15/755,595, filed as application No. PCT/IB2016/055204 on Aug. 31, 2016, now abandoned.

(60) Provisional application No. 62/212,058, filed on Aug. 31, 2015.

(51) **Int. Cl.**

C07K 14/71	(2006.01)
A61P 35/00	(2006.01)
C07K 16/22	(2006.01)
A61K 39/00	(2006.01)

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

CPC ***C07K 14/71*** (2013.01); ***A61P 35/00*** (2018.01); ***C07K 16/22*** (2013.01); *A61K 2039/505* (2013.01); *C07K 2317/94* (2013.01); *C07K 2319/30* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Gary B Nickol
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(57) **ABSTRACT**

The present invention relates, in general, to polypeptides capable of binding and neutralizing transforming growth factor beta (TGF-beta) ligands, and uses of these polypeptides for treating disorders related to TGF-beta expression or activation (e.g. cancer and fibrotic diseases), and methods of making such molecules.

14 Claims, 30 Drawing Sheets

Specification includes a Sequence Listing.

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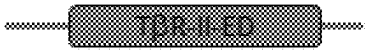

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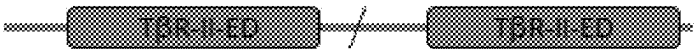
T22d35



IPPHVQKSVNNDMIVTDNNGAVKFP**QLCKFCDVRFSTCDNQKSCMSNCSITSICEKP QEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMC SCSSDECNDNIIF**SEEYNTSNPDIPPHVQKSVNNDMIVTDNNGAVKFP**QLCKFCDVR FSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILE DAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIF**SEEYNTSNPD

FIG. 1A

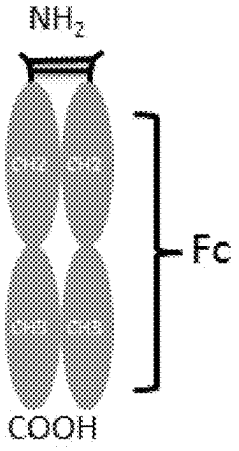


FIG. 1B

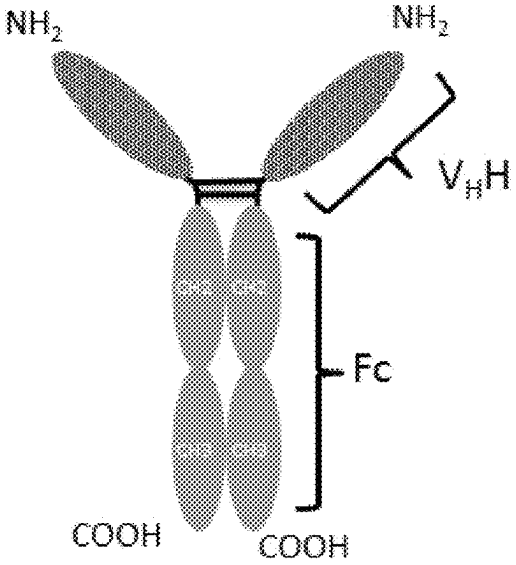


FIG. 1C

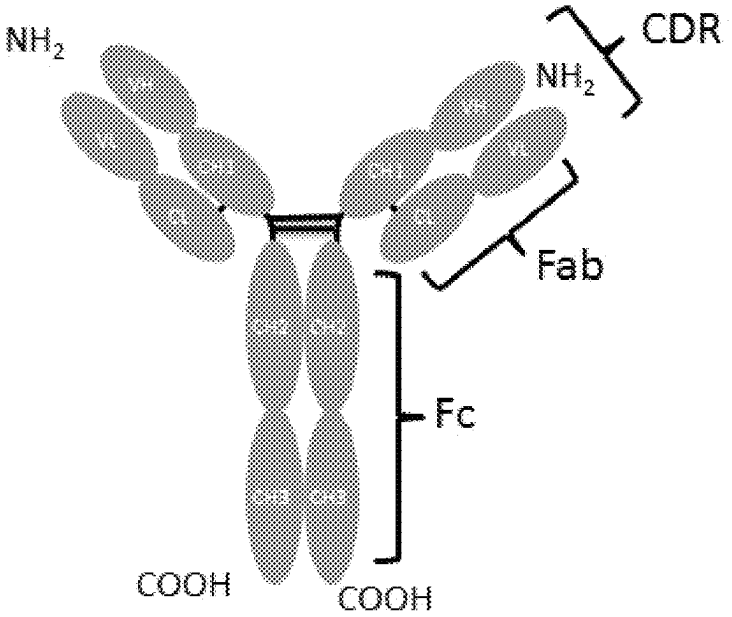


FIG. 1D

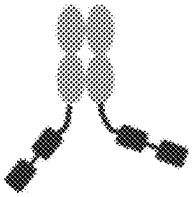


FIG. 2A

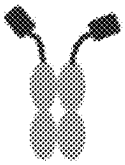


FIG. 2B

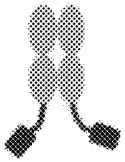


FIG. 2C

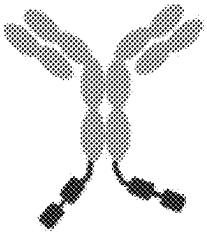


FIG. 2D

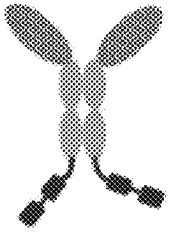


FIG. 2E

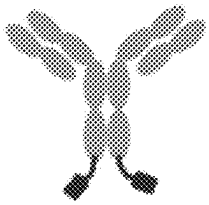


FIG. 2F

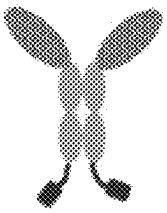


FIG. 2G

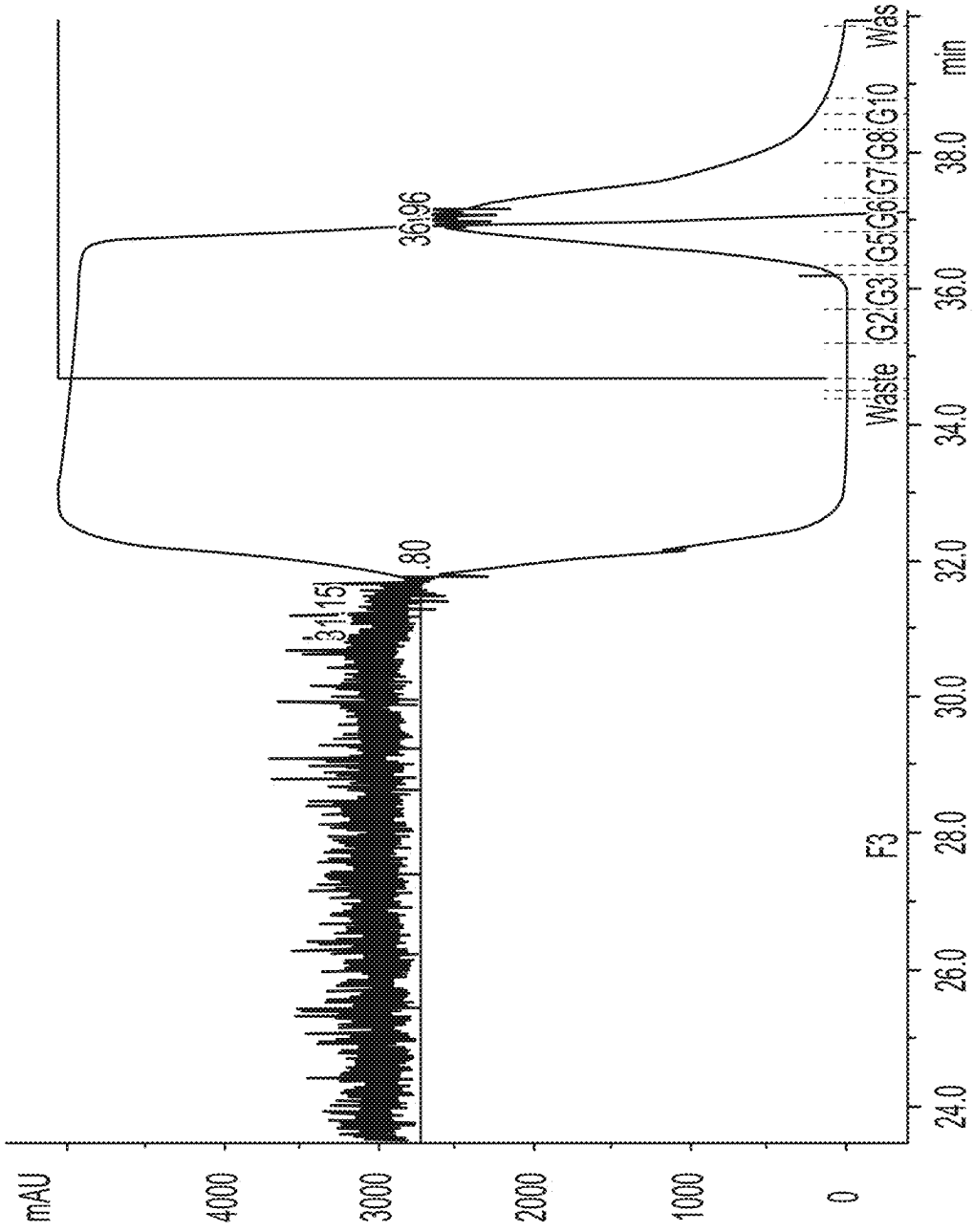

mAU
4000
3000
2000
1000
0
24.0
26.0
28.0
30.0
32.0
34.0
36.0
38.0
min
F3
31.15
.80
36.96
Waste
G2
G3
G5
G6
G7
G8
G10
Was

FIG. 3A

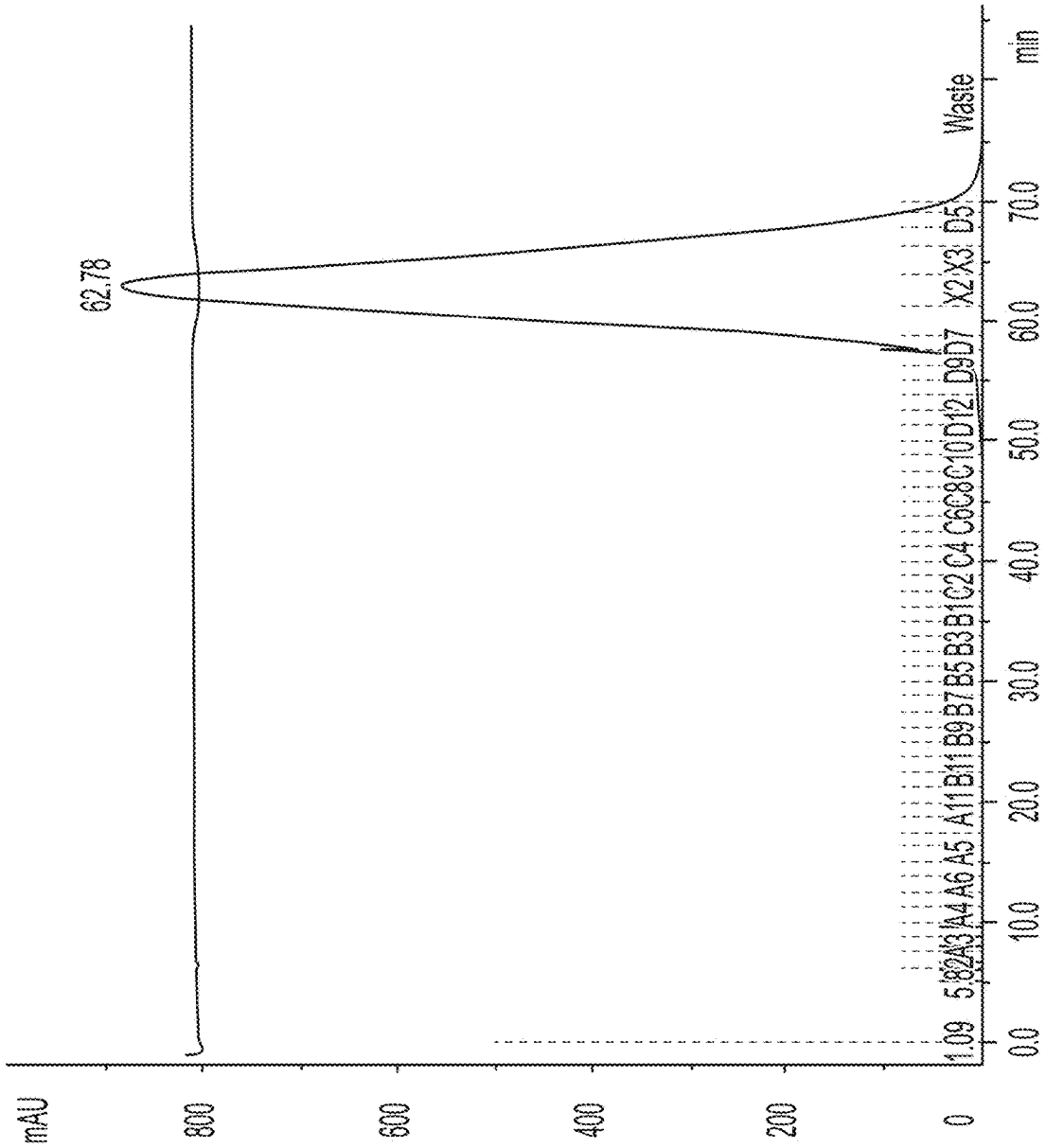

mAU
800
600
400
200
0
62.78
1.09
5.82
A3
A4
A6
A5
A11
B11
B9
B7
B5
B3
B1
C2
C4
C6
C8
C10
D12
D9
D7
X2
X3
D5
Waste
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
min

FIG. 3B

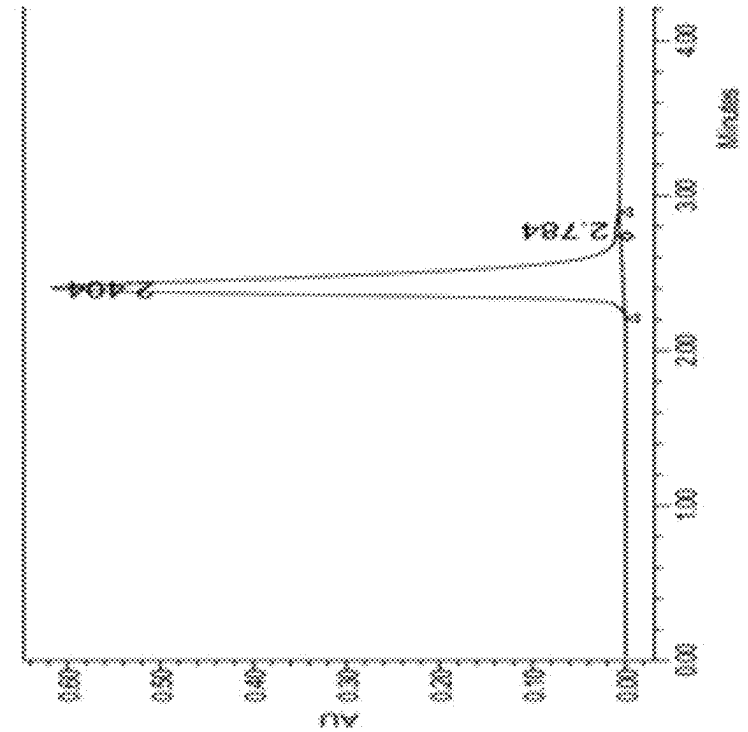

0.60
0.50
0.40
0.30
0.20
0.10
0.00
AU
0.00
1.00
2.00
3.00
4.00
Minutes
2.104
2.784

FIG. 3D

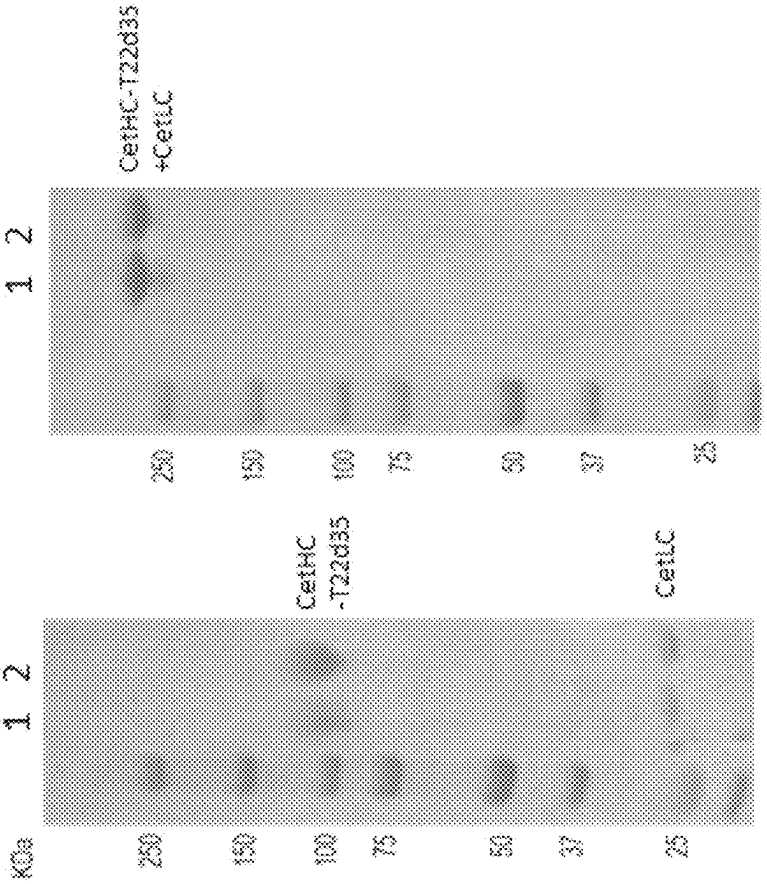

1 2
CetHC-T22d35
+CetLC
250
150
100
75
50
37
25
1 2
KDa
CetHC
-T22d35
CetLC
250
150
100
75
50
37
25

FIG. 3C

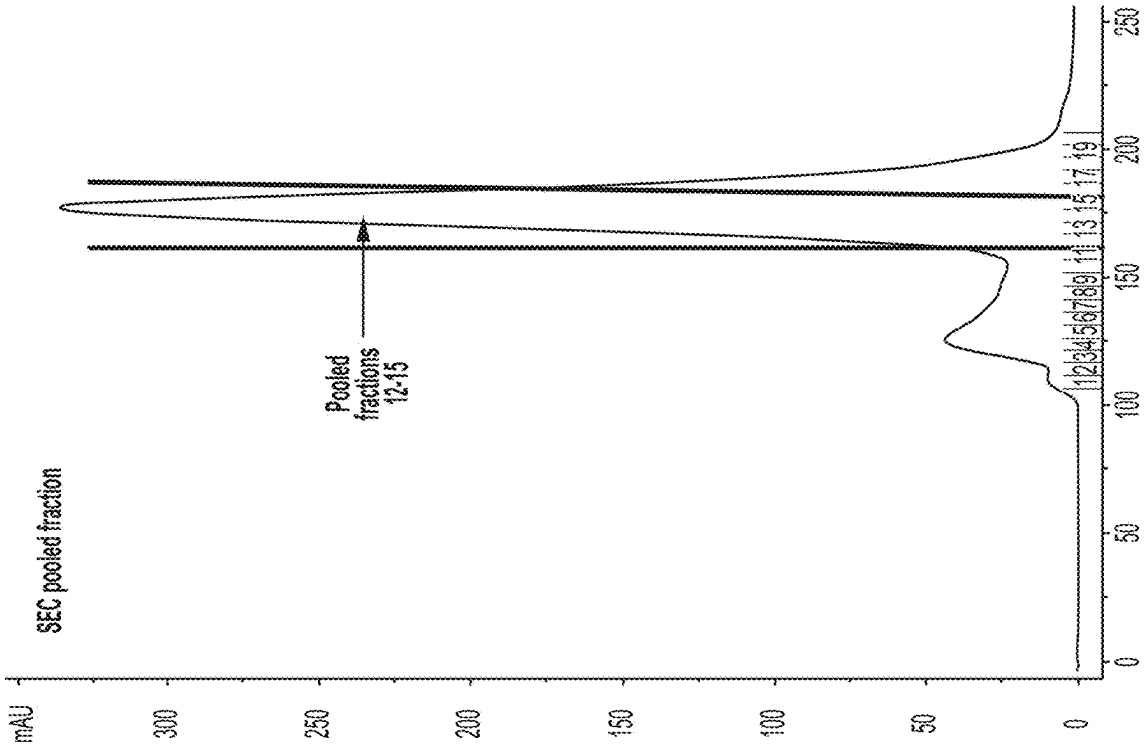
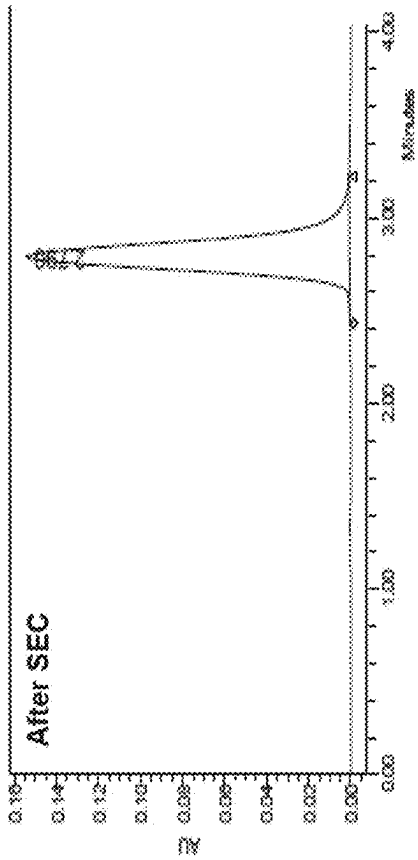
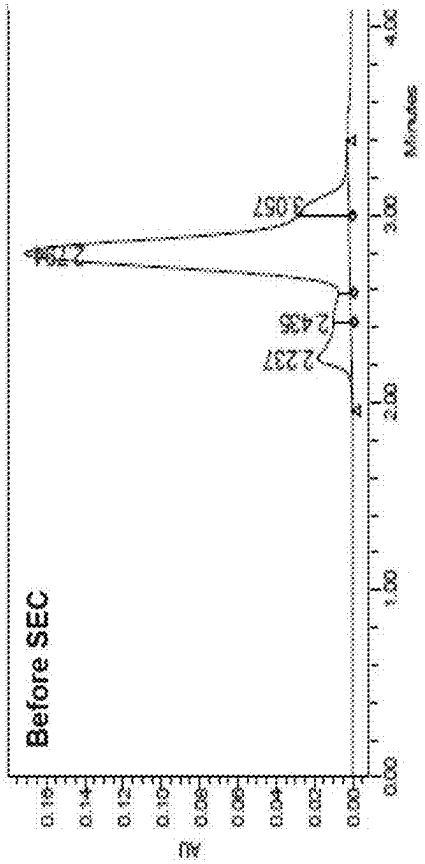

SEC pooled fraction
mAU
300
250
200
150
100
50
0
Pooled fractions 12-15
0
50
100
150
200
250
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

FIG. 3E



	RT	Area	% Area	Height
1	2.790	1622265	100.00	153621

FIG. 3G



	RT	Area	% Area	Height
1	2.237	195821	8.27	17877
2	2.435	73859	3.12	9131
3	2.794	1917399	80.99	169299
4	3.057	180323	7.62	21365

FIG. 3F

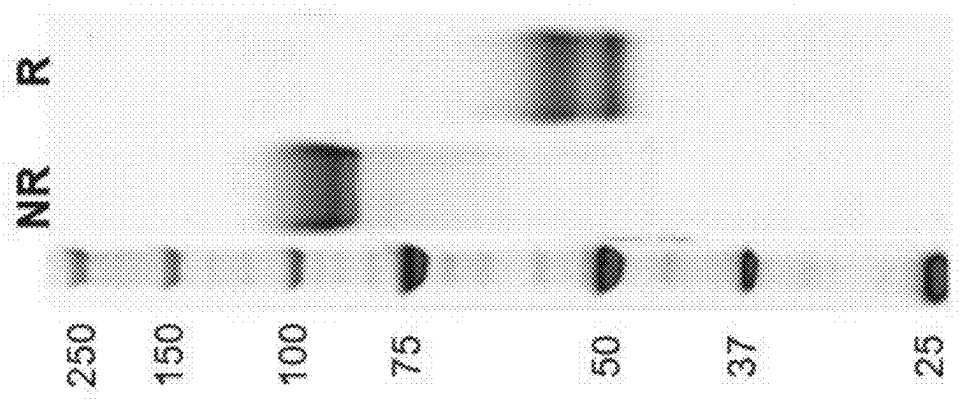


FIG. 3H

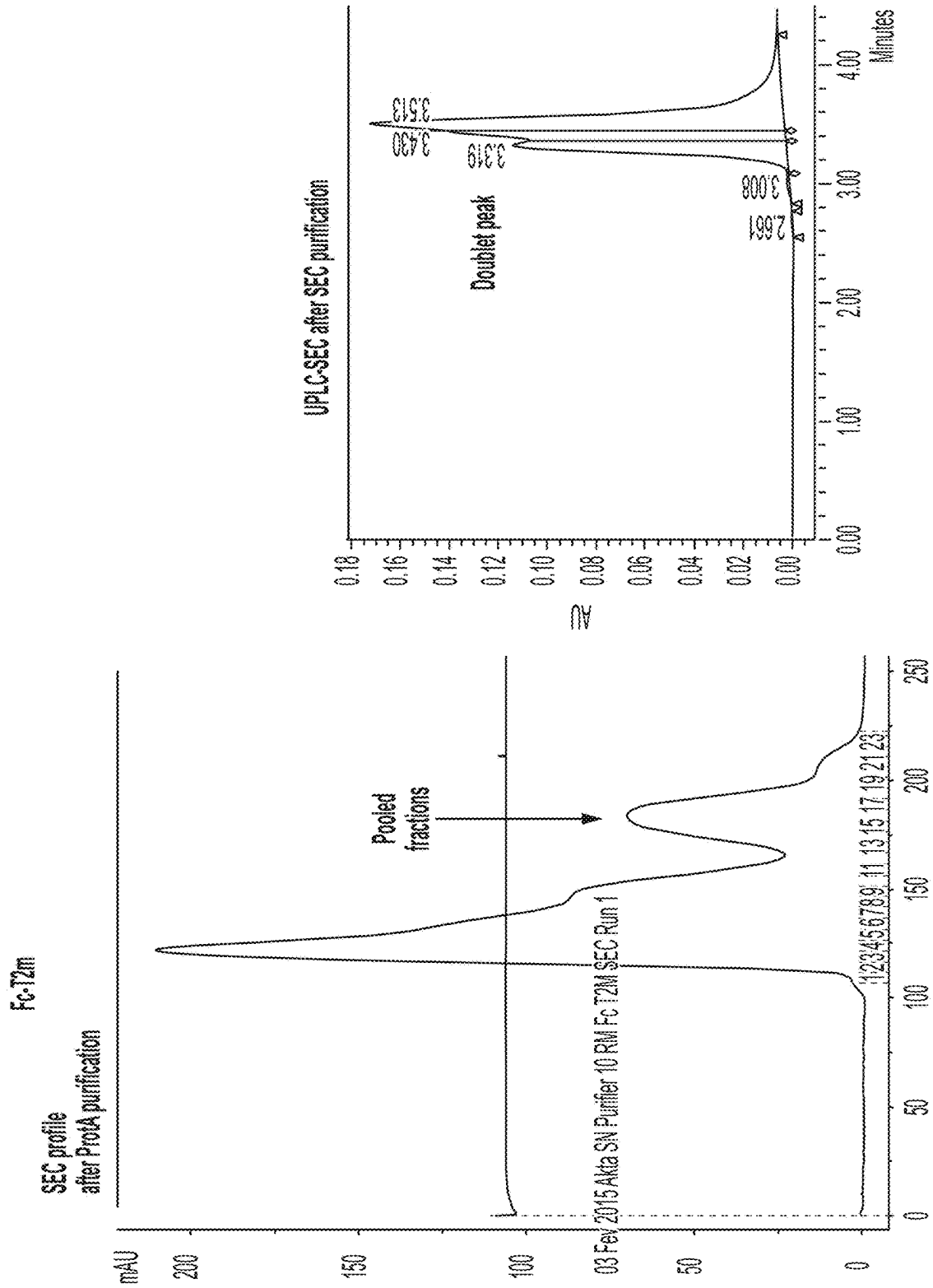

Fc-T2m
SEC profile
after ProtA purification
mAU
200
150
100
50
0
03 Fev 2015 Akta SN Purifier 10 RM Fc T2M SEC Run 1
Pooled
fractions
1 2 3 4 5 6 7 8 9 11 13 15 17 19 21 23
0
50
100
150
200
250
UPLC-SEC after SEC purification
AU
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Doublet peak
3.513
3.430
3.319
3.008
2.661
0.00
1.00
2.00
3.00
4.00
Minutes

FIG. 3I

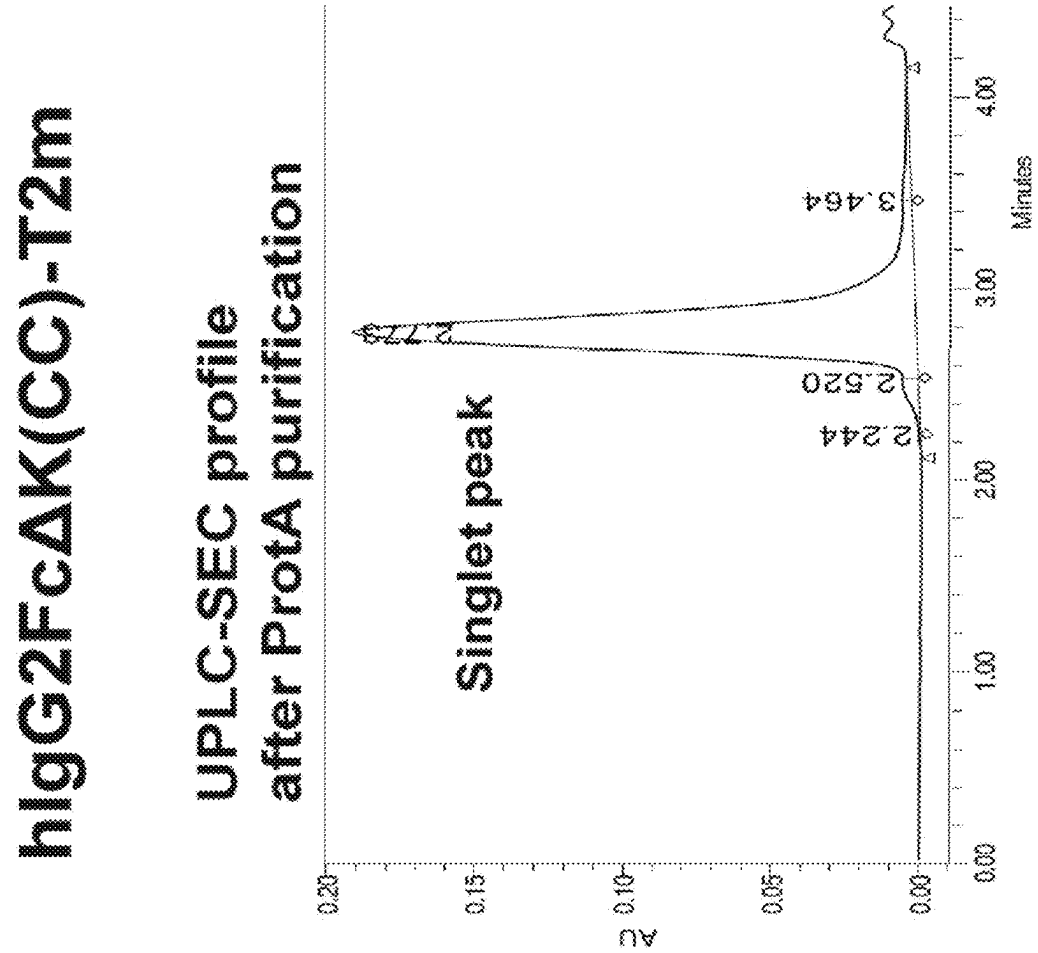

hIgG2FcΔK(CC)-T2m
UPLC-SEC profile
after ProtA purification
Singlet peak
2.244
2.520
2.773
3.464
AU
0.20
0.15
0.10
0.05
0.00
0.00
1.00
2.00
3.00
4.00
Minutes

FIG. 3J

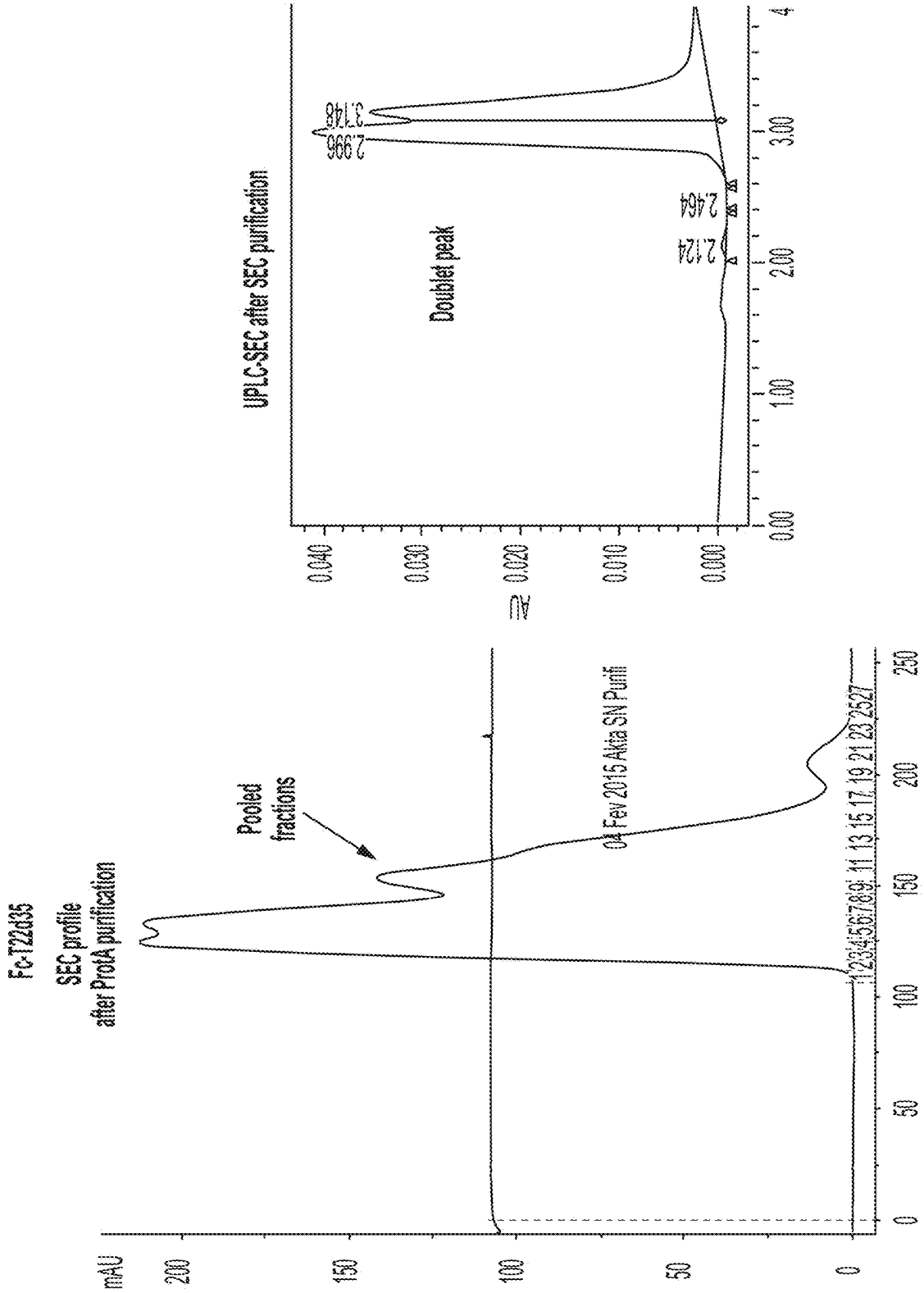

Fc-T22d35
SEC profile
after ProtA purification
mAU
200
150
100
50
0
Pooled
fractions
04 Fev 2015 Akta SN Purifi
0
50
100
150
200
250
UPLC-SEC after SEC purification
Doublet peak
3.148
2.996
2.464
2.124
0.040
0.030
0.020
0.010
0.000
0.00
1.00
2.00
3.00
4

FIG. 3K

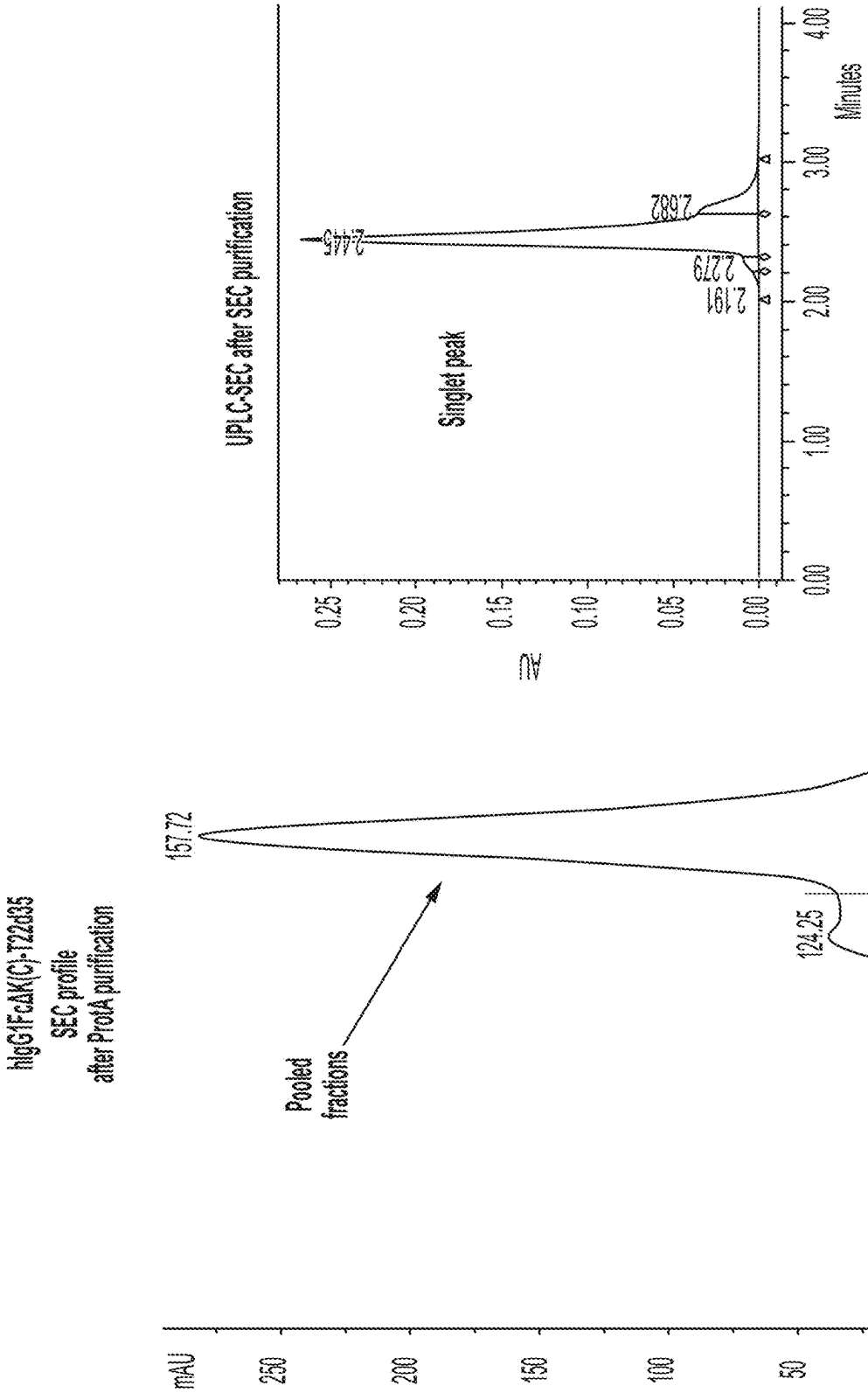

hIgG1FcAK(C)-T22d35
SEC profile
after ProtA purification
mAU
250
200
150
100
50
0
157.72
124.25
Pooled fractions
0
50
100
150
200
1 2 3 4 5 6 7 8 9 10 12 14 16 18
UPLC-SEC after SEC purification
Singlet peak
2.446
2.682
2.191
2.279
AU
0.25
0.20
0.15
0.10
0.05
0.00
0.00
1.00
2.00
3.00
4.00
Minutes

FIG. 3L

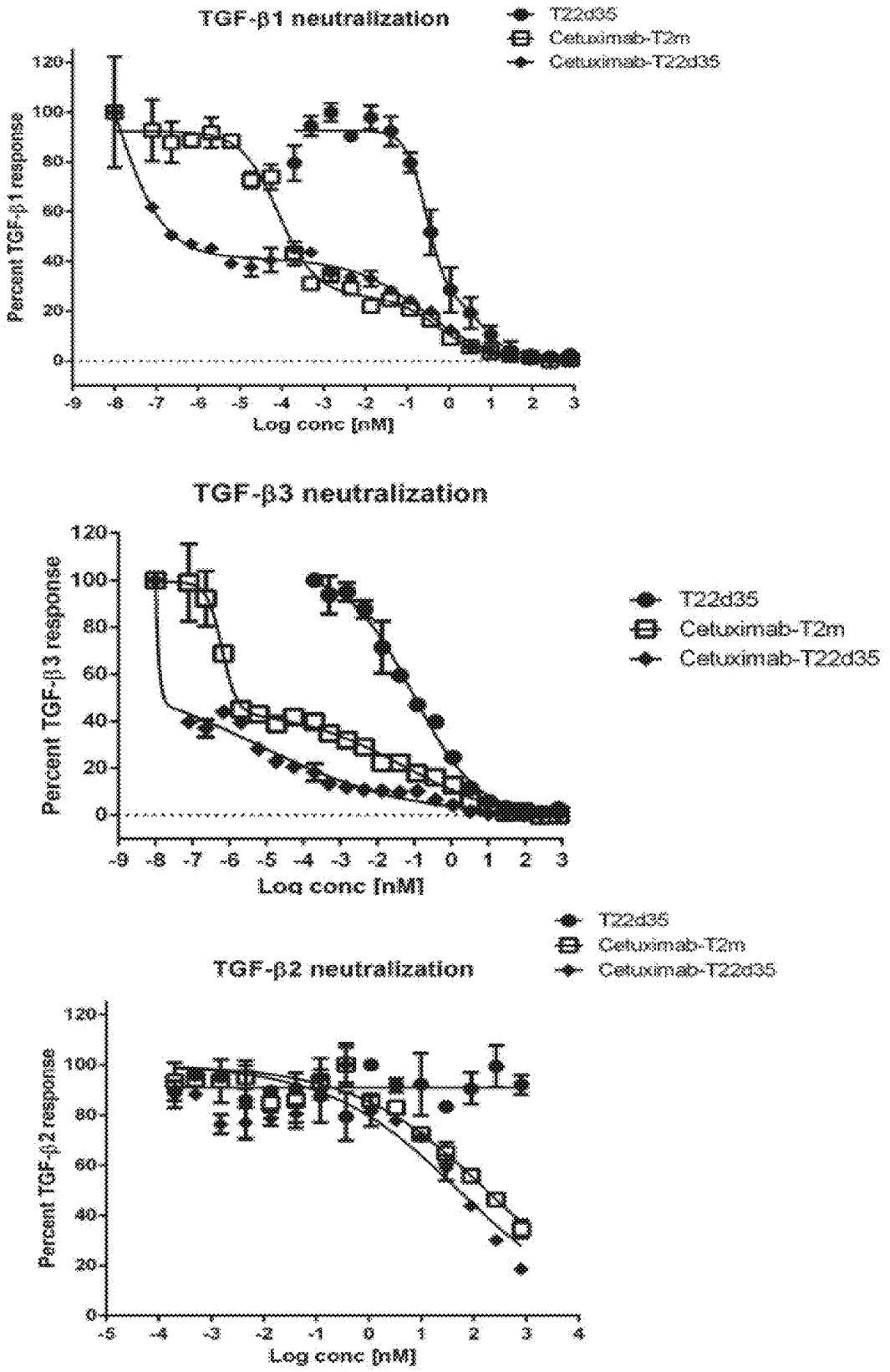
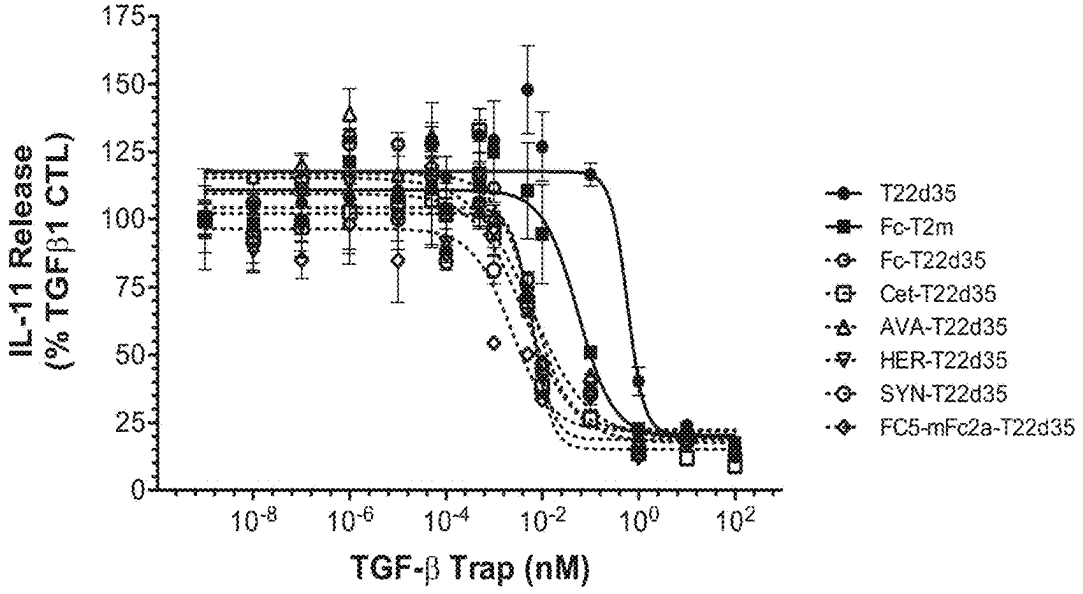
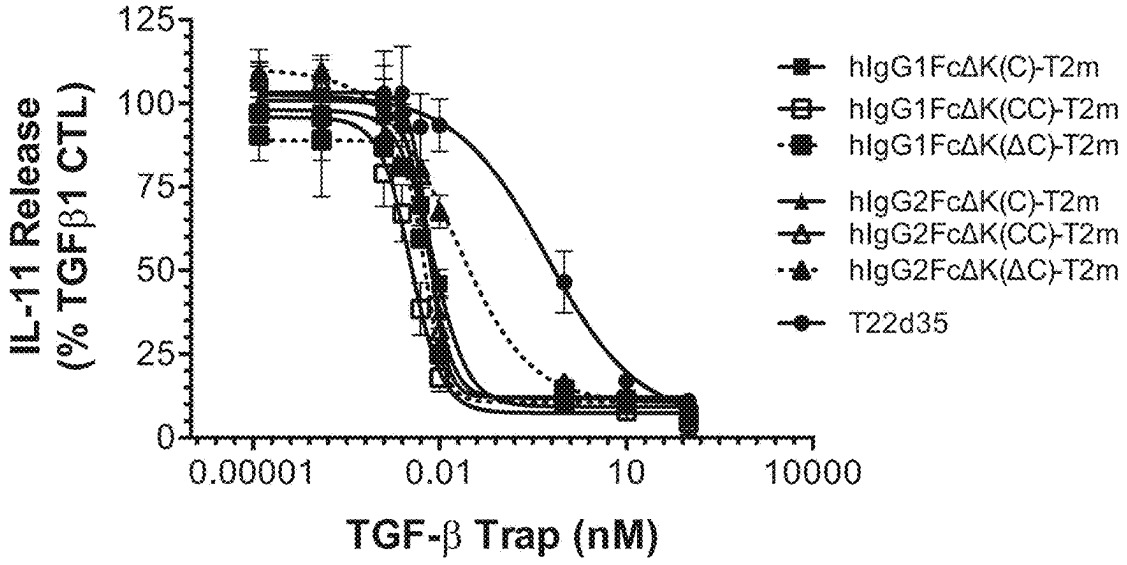

TGF-β1 neutralization
T22d35
Cetuximab-T2m
Cetuximab-T22d35
Percent TGF-β1 response
Log conc [nM]
TGF-β3 neutralization
Percent TGF-β3 response
Log conc [nM]
TGF-β2 neutralization
Percent TGF-β2 response
Log conc [nM]

FIG. 4A



	T22d35	Fc-T2m	Fc-T22d35	Cet-T22d35	AVA-T22d35	HER-T22d35	SYN-T22d35	FC5-mFc2a-T22d35
IC50	0.5796	0.05546	0.00617	0.005753	0.005935	0.006482	0.004591	0.005733
Fold Change T22d35	1	10	94	101	98	89	126	101
Fold Change Fc-T2m	0.1	1	9	10	9	9	12	10

FIG. 4B



	TGF-β1						
	T22d35	hIgG1Fc (ΔC)ΔK-T2m	hIgG1Fc ΔK(CC)-T2m	hIgG1Fc ΔK(C)-T2m	hIgG2Fc (ΔC)ΔK-T2m	hIgG2Fc ΔK(CC)-T2m	hIgG2Fc ΔK(C)-T2m
IC50	0.5257	0.005903	0.003487	0.007894	0.01698	0.006694	0.006612
Fold Change T22d35	1	89	151	67	31	79	80

FIG. 4C

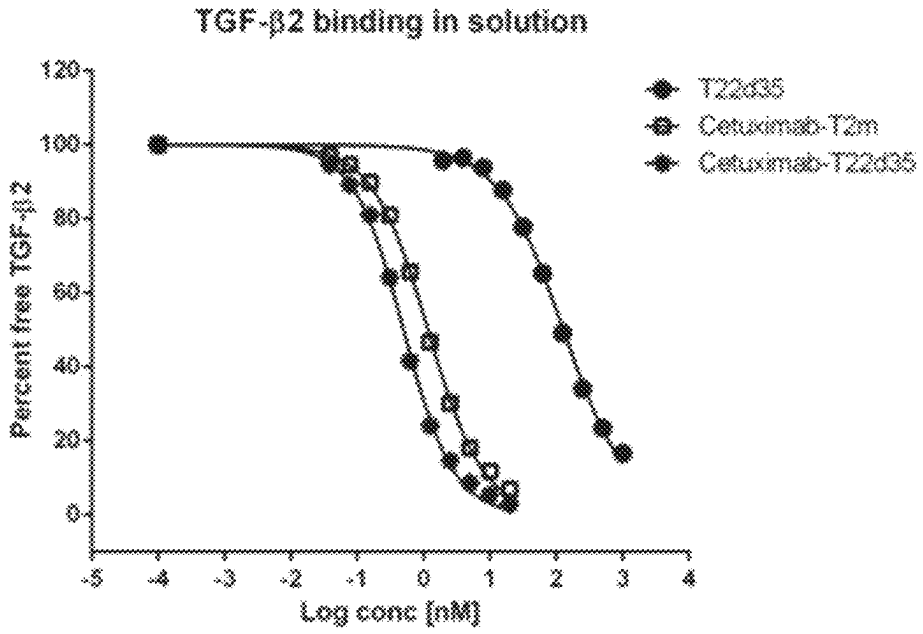

TGF-β2 binding in solution
T22d35
Cetuximab-T2m
Cetuximab-T22d35
Percent free TGF-β2
120
100
80
60
40
20
0
-5
-4
-3
-2
-1
0
1
2
3
4
Log conc [nM]

FIG. 4D

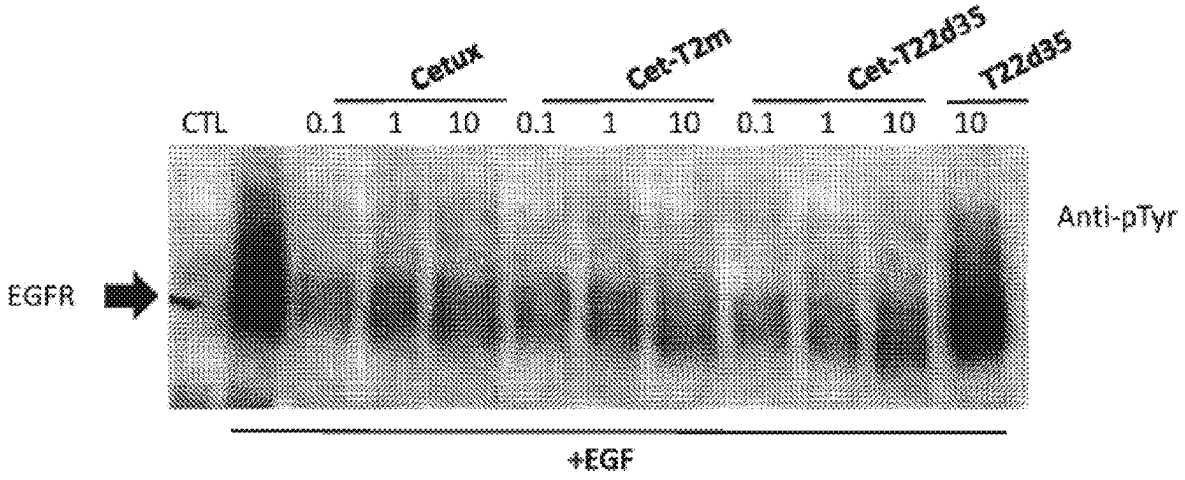

Cetux
Cet-T2m
Cet-T22d35
T22d35
CTL
0.1
1
10
0.1
1
10
0.1
1
10
10
Anti-pTyr
EGFR
+EGF

FIG. 5A

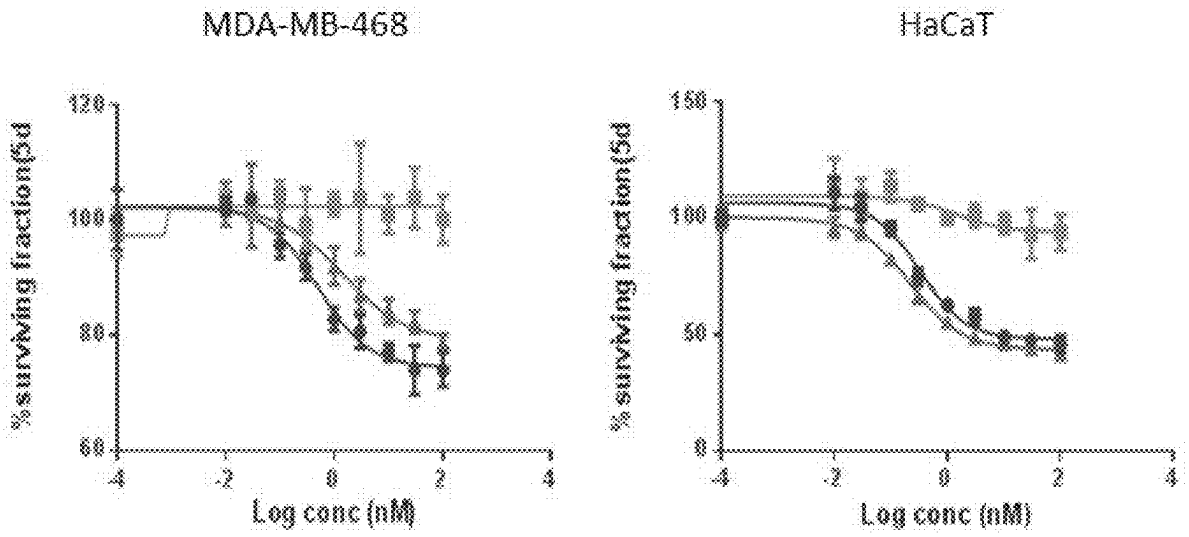

MDA-MB-468
HaCaT
% surviving fraction(5d
120
100
80
60
150
100
50
0
-4
-2
0
2
4
Log conc (nM)

FIG. 5B

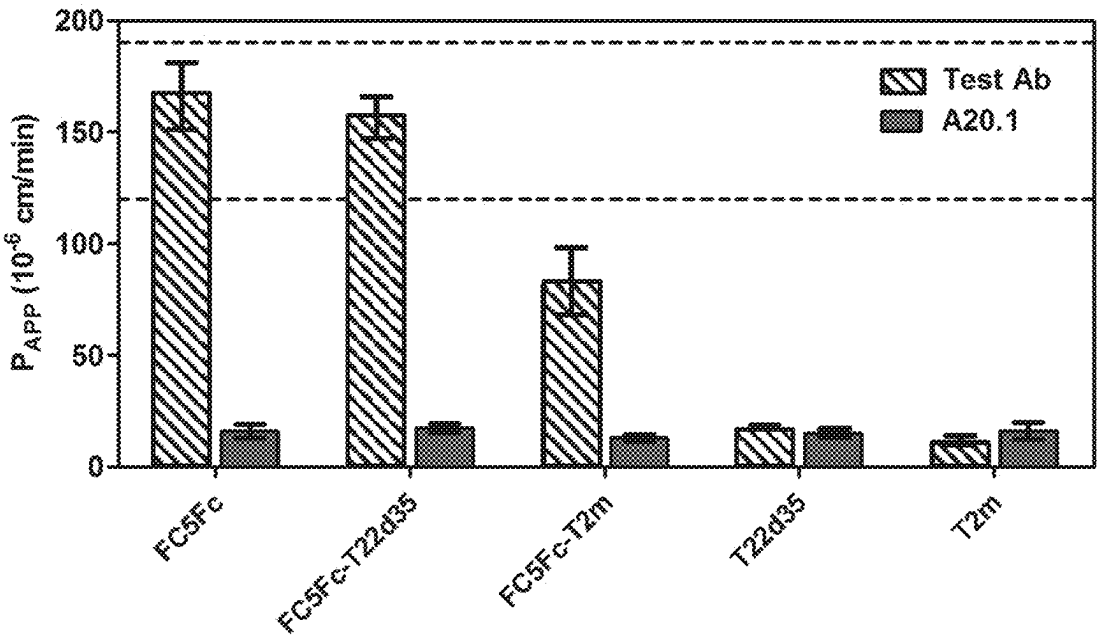

200
150
100
50
0
P_{APP} (10^{-6} cm/min)
Test Ab
A20.1
FC5Fc
FC5Fc-T22d35
FC5Fc-T2m
T22d35
T2m

FIG. 6

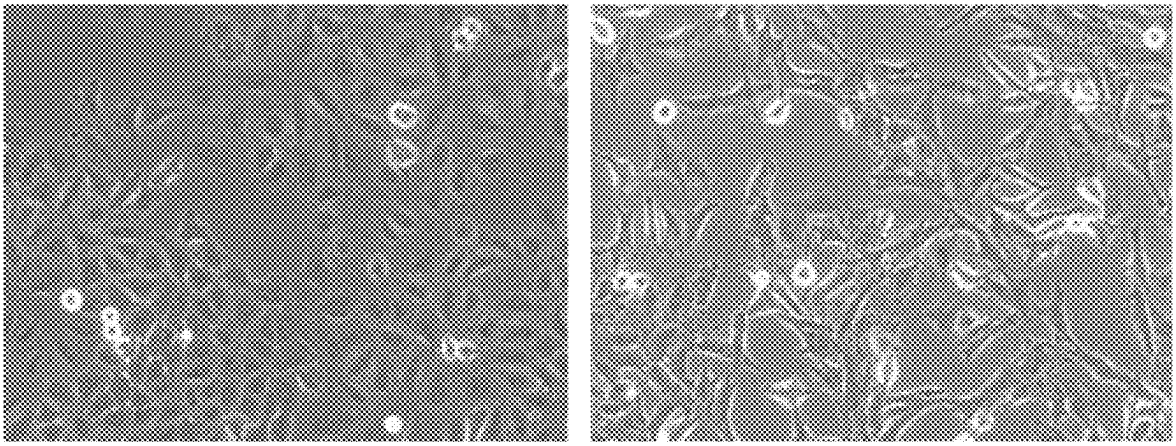


FIG. 7A

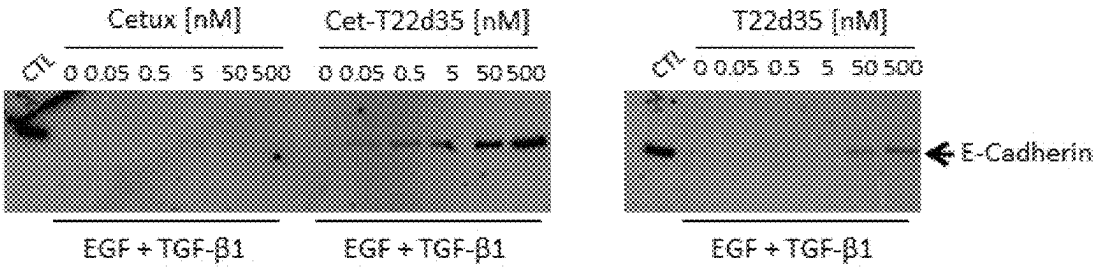

Cetux [nM]
Cet-T22d35 [nM]
T22d35 [nM]
Ctl
0 0.05 0.5 5 50 500
0 0.05 0.5 5 50 500
Ctl
0 0.05 0.5 5 50 500
E-Cadherin
EGF + TGF-β1
EGF + TGF-β1
EGF + TGF-β1

FIG. 7B

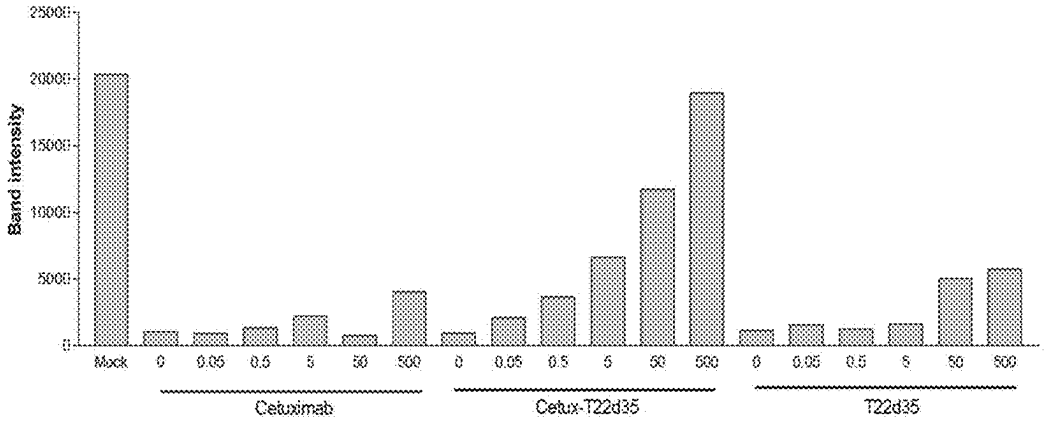
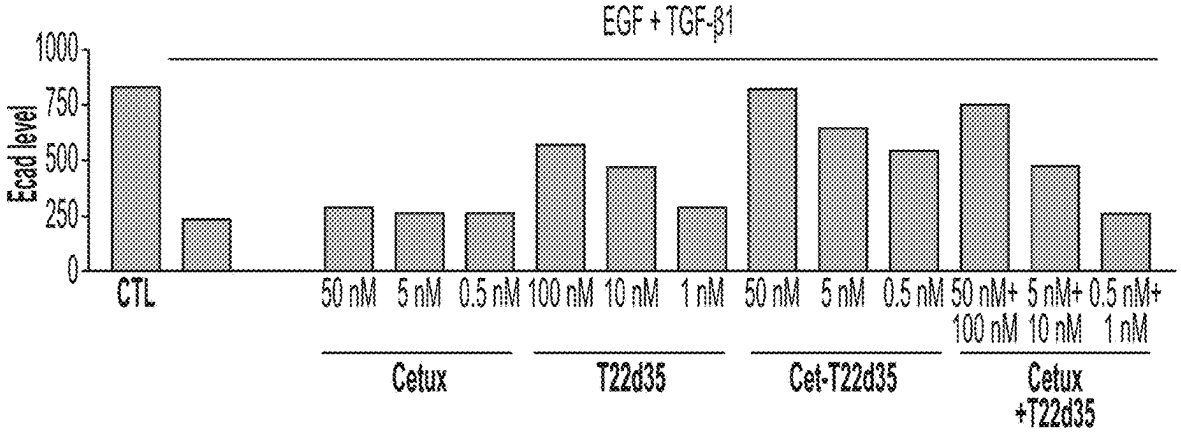

Band intensity
25000
20000
15000
10000
5000
0
Mock
0
0.05
0.5
5
50
500
Cetuximab
Cetux-T22d35
T22d35

FIG. 7C


EGF + TGF-β1
Ecad level
1000
750
500
250
0
CTL
50 nM
5 nM
0.5 nM
100 nM
10 nM
1 nM
50 nM
5 nM
0.5 nM
50 nM+ 100 nM
5 nM+ 10 nM
0.5 nM+ 1 nM
Cetux
T22d35
Cet-T22d35
Cetux +T22d35

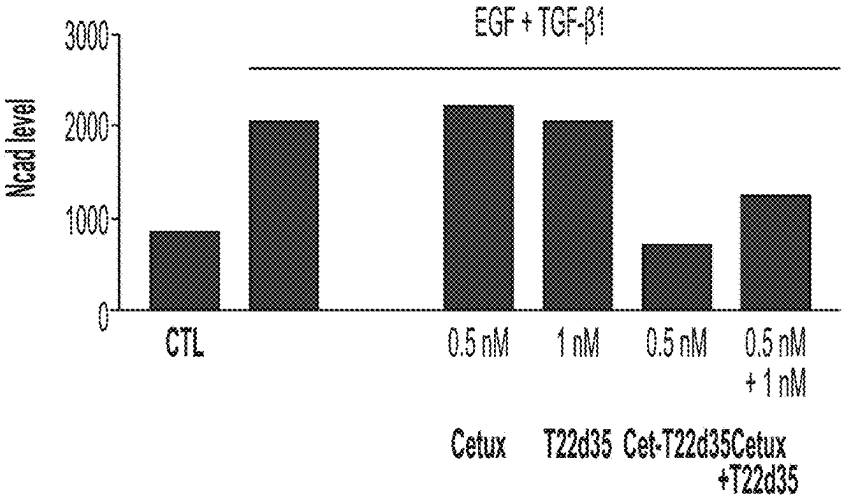

EGF + TGF-β1
Ncad level
3000
2000
1000
0
CTL
0.5 nM
1 nM
0.5 nM
0.5 nM + 1 nM
Cetux
T22d35
Cet-T22d35
Cetux +T22d35

FIG. 7D

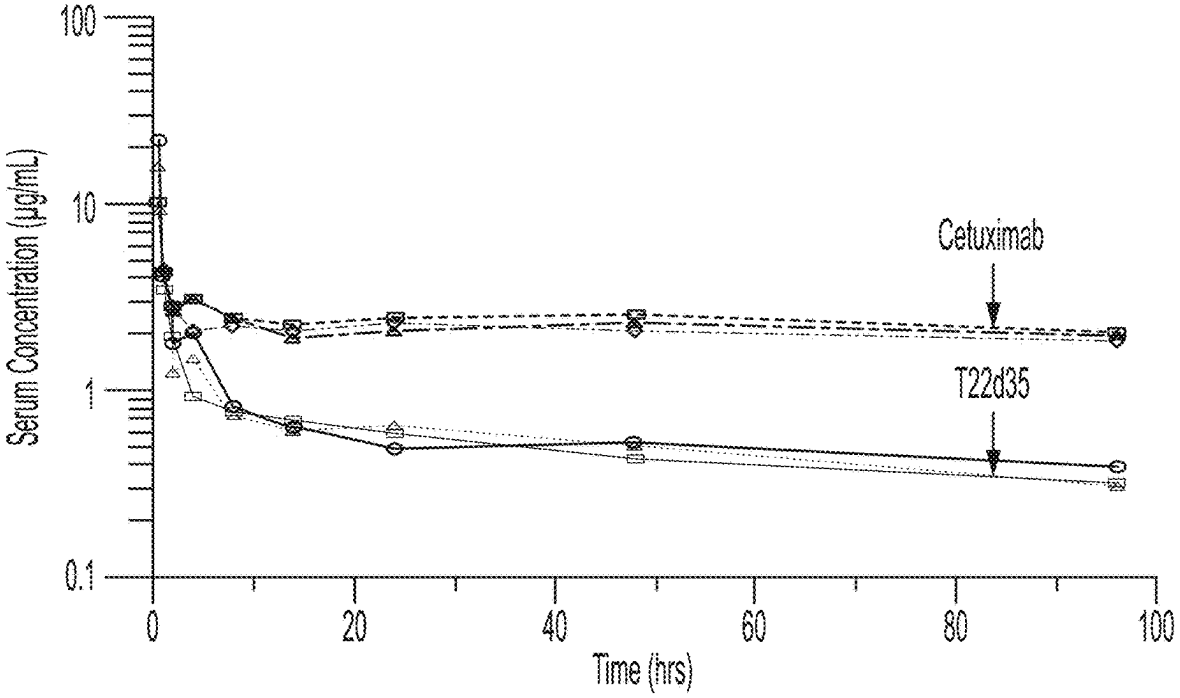
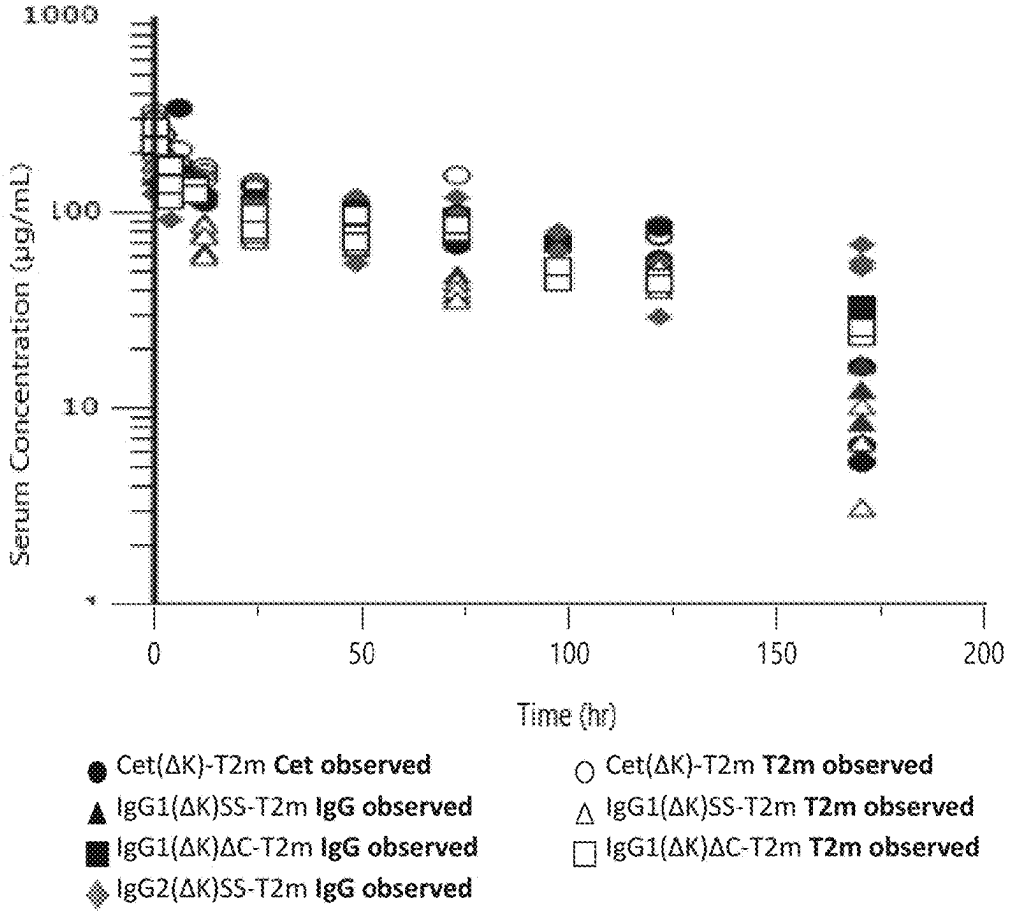
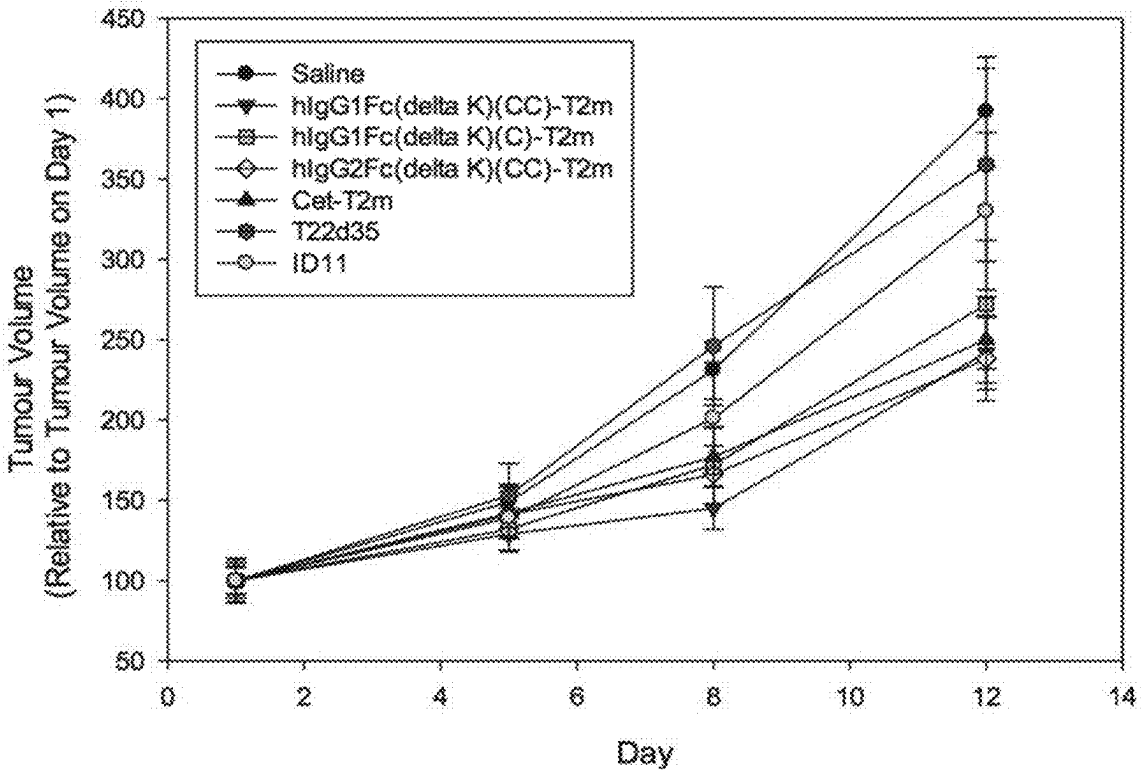

100
10
1
0.1
Serum Concentration (µg/mL)
0
20
40
60
80
100
Time (hrs)
Cetuximab
T22d35

FIG. 8A



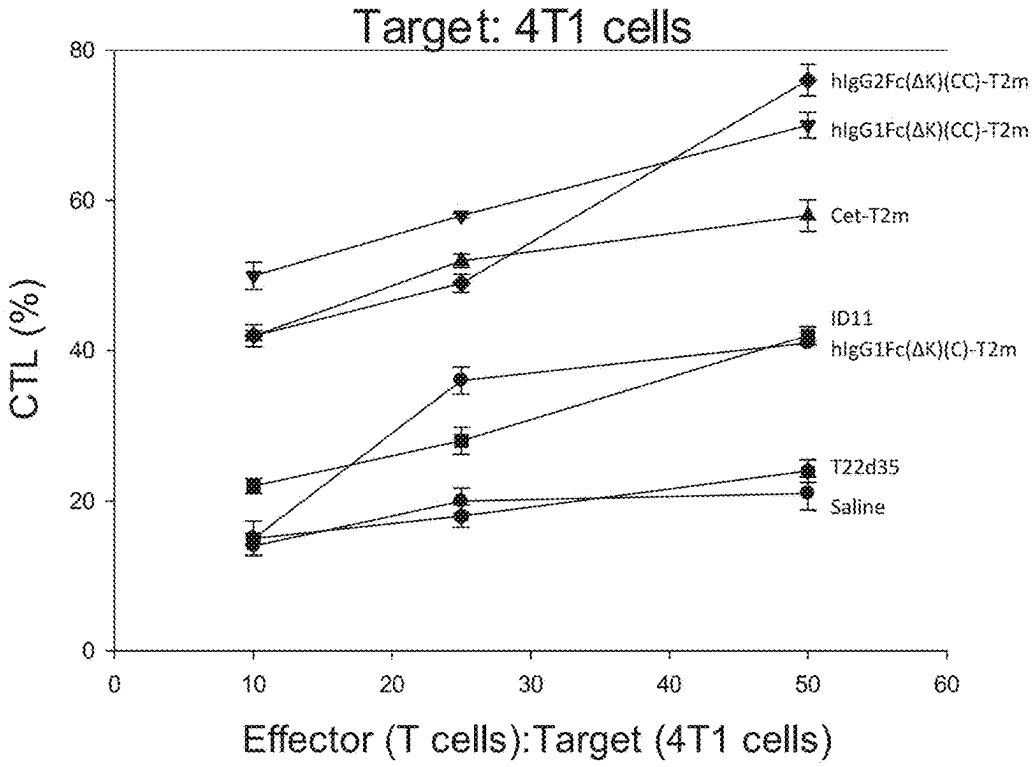
PK Parameter	Units	Cetuximab (ΔK)-T2m (Fc_peptide: ALP)		Cetuximab (ΔK)-T2m (Trap_peptide: LPY)		IgG1Fc(ΔC)ΔK-T2m (Fc_peptide: ALP)		IgG1Fc(ΔC)ΔK-T2m (Trap_peptide: LPY)		IgG2Fc(SS)ΔK-T2m (Trap_peptide: LPY)	
		Estimate	CV%	Estimate	CV%	Estimate	CV%	Estimate	CV%	Estimate	CV%
Alpha_hl	hr	2.1	5.94	3.07	11.54	1.4	22.06	1.36	34.19	4.4	57.18
Beta_hl	**hr**	**99.04**	**11.48**	**119.84**	**19.04**	**103.47**	**6.47**	**90.14**	**31.6**	**125.31**	**14.64**
AUC	µg.hr/mL	20142.9	7.39	27455.2	18.81	18437.3	2.11	15265.6	16	24343.2	7.79
Cmax	µg/mL	275.48	11.35	309.05	1.79	270.33	2.05	256.88	11.44	171.09	15
MRT	hr	140	11.85	168.7	19.61	146.88	6.29	127.71	31.18	179.07	13.87
VSS	mL/kg	69.5	5.61	61.45	1.68	79.66	6.74	83.66	17.48	73.56	11.48
Cl	mL/hr/kg	0.5	7.39	0.36	18.81	0.54	2.11	0.66	16	0.41	7.79
Cl2	mL/hr/kg	5.6	3.88	3.37	11.78	9.64	21.71	10.4	27.45	1.87	10.02
V1	mL/kg	36.3	11.35	32.36	1.79	36.99	2.05	38.93	11.44	58.45	15
V2	mL/kg	33.2	0.98	29.09	2.5	42.67	12.31	44.73	35.81	15.11	80.4

FIG. 8B



Statistical comparison	p-value
Saline vs hIgG1Fc(delta K)(CC)-T2m	p=0.003
Saline vs hIgG1Fc(delta K)(C)-T2m	p=0.05
Saline vs hIgG2Fc(delta K)(CC)-T2m	p=0.003
Saline vs Cet-T2m	p=0.007
Saline vs T22d35	ns (p=0.671)
Saline vs ID11	ns (p=0.353)

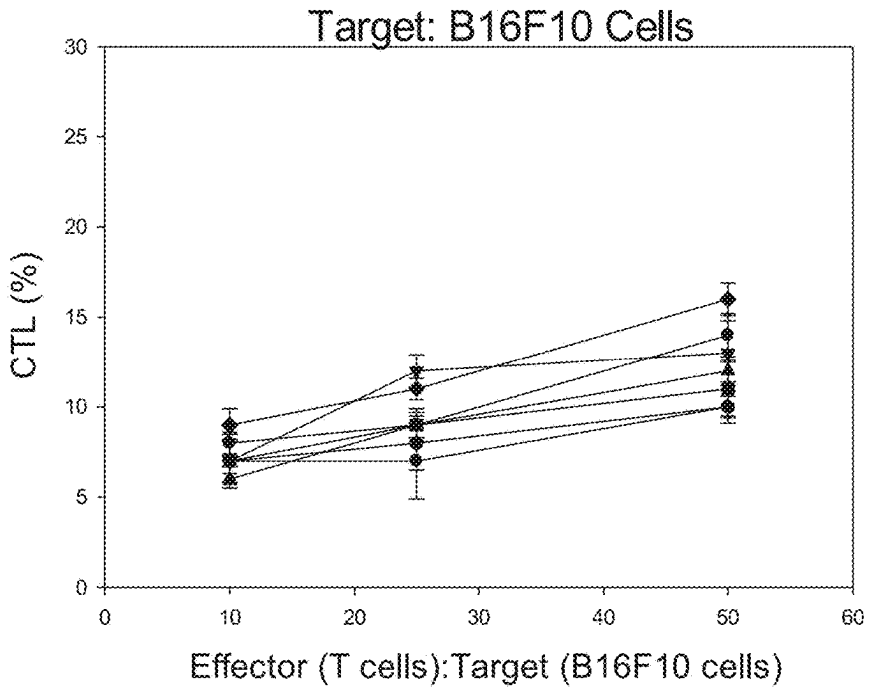
FIG. 9A



Column	
1	Effector (T cell):Target (4T1 cell) ratio
2	Saline (mean of 3 independent measurements ± SEM)
3	hIgG1Fc(ΔK)(CC)-T2m (mean of 3 independent measurements ± SEM)
4	hIgG1Fc(ΔK)(C)-T2m (mean of 3 independent measurements ± SEM)
5	hIgG2Fc(ΔK)(CC)-T2m (mean of 3 independent measurements ± SEM)
6	Cet-T2m (mean of 3 independent measurements ± SEM)
7	T22d35 (mean of 3 independent measurements ± SEM)
8	ID11 (mean of 3 independent measurements ± SEM)

		1	2	3	4	5	6	7	8
Effector cell:Target cell Ratio	10	14±1.2	50±1.8	22±1.0	42±1.5	42±0.7	15±2.3	15±0.7
	25	20±1.7	58±0.3	28±1.8	49±1.2	52±0.9	18±1.5	36±1.8
	50	21±2.2	70±1.7	42±1.2	76±2.1	58±2.1	24±1.5	41±0.3

FIG. 9B



All symbols are as shown for Fig. 9B

Column	
1	Effector (T cell):Target (B16F10 cell) ratio
2	Saline (mean of 3 independent measurements ± SEM)
3	hIgG1Fc(ΔK)(CC)-T2m (mean of 3 independent measurements ± SEM)
4	hIgG1Fc(ΔK)(C)-T2m (mean of 3 independent measurements ± SEM)
5	hIgG2Fc(ΔK)(CC)-T2m (mean of 3 independent measurements ± SEM)
6	Cet-T2m (mean of 3 independent measurements ± SEM)
7	T22d35 (mean of 3 independent measurements ± SEM)
8	ID11 (mean of 3 independent measurements ± SEM)

	1	2	3	4	5	6	7	8
Effector cell:Target cell Ratio	10	7±0.3	7±1.5	7±1.2	9±0.9	6±0.3	7±0.3	8±0.6
	25	7±2.1	12±0.9	9±0.3	11±0.6	9±0.9	8±1.5	9±0.7
	50	10±0.9	13±1.8	11±1.5	16±0.9	12±0.6	10±0.6	14±1.2

FIG. 9C

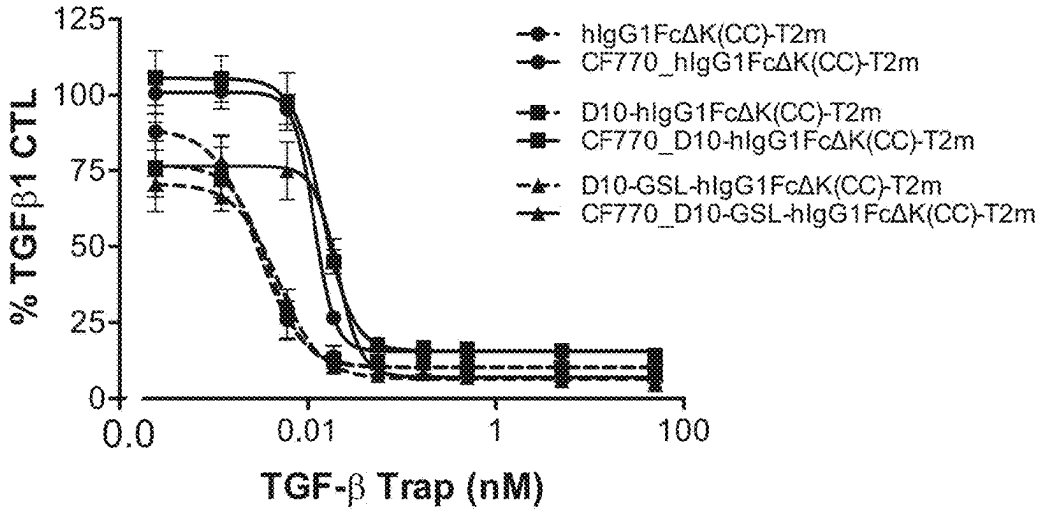
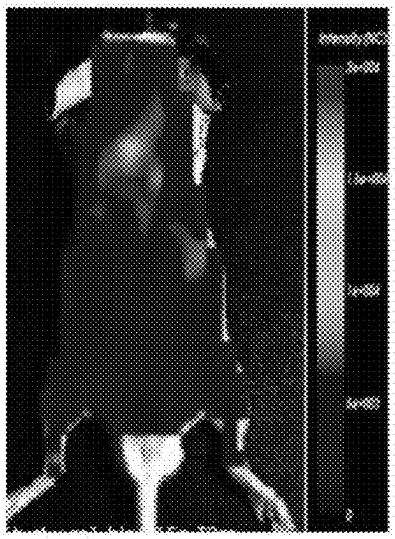


FIG. 10A

	hIgG1FcΔK(CC)-T2m	D10-hIgG1FcΔK(CC)-T2m	D10-GSL-hIgG1FcΔK(CC)-T2m
IC50	0.002895	0.003794	0.004855
	CF770_hIgG1FcΔK(CC)-T2m	CF770_D10-hIgG1FcΔK(CC)-T2m	CF770_D10-GSL-hIgG1FcΔK(CC)-T2m
IC50	0.01172	0.01453	0.02093

FIG. 10B

hIgG1FcΔK(CC)-T2m



D10-hIgG1FcΔK(CC)-T2m

D10-GSL-hIgG1FcΔK(CC)-T2m

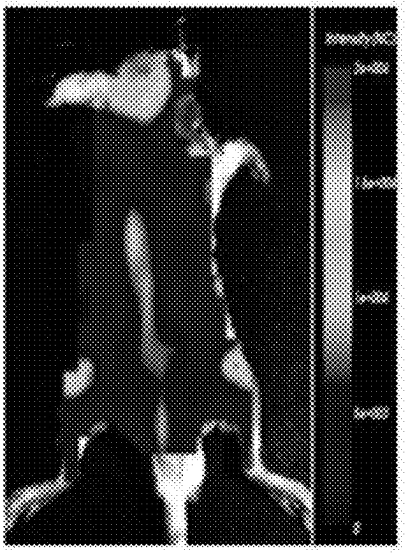


FIG. 10C

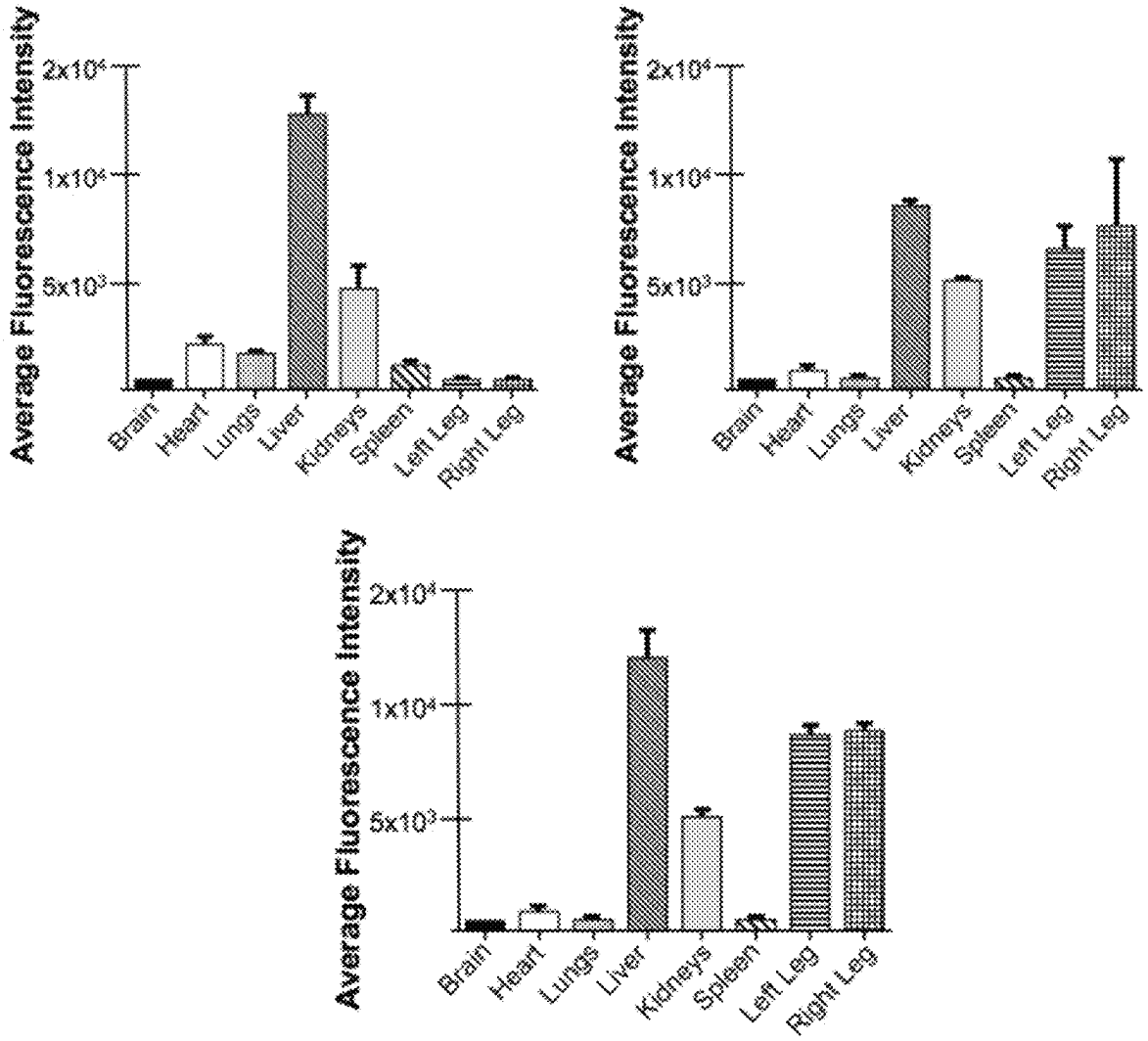

Average Fluorescence Intensity
2x10⁴
1x10⁴
5x10³
Brain
Heart
Lungs
Liver
Kidneys
Spleen
Left Leg
Right Leg
Average Fluorescence Intensity
2x10⁴
1x10⁴
5x10³
Brain
Heart
Lungs
Liver
Kidneys
Spleen
Left Leg
Right Leg
Average Fluorescence Intensity
2x10⁴
1x10⁴
5x10³
Brain
Heart
Lungs
Liver
Kidneys
Spleen
Left Leg
Right Leg

FIG. 10D

TGF-β-RECEPTOR ECTODOMAIN FUSION MOLECULES AND USES THEREOF

RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 15/755,595, filed Feb. 27, 2018, which is a national stage filing under 35 U.S.C. § 371 of International Application No. PCT/IB2016/055204, filed Aug. 31, 2016, and claims the benefit under 35 U.S.C. § 119(e) of U.S. provisional application Ser. No. 62/212,058, filed Aug. 31, 2015, the entire contents of each of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to TGF-β superfamily receptor ectodomain fusion molecules and uses thereof. More specifically, the present invention relates to TGF-β superfamily receptor ectodomain fusion molecules and their use in TGF-β superfamily ligand neutralization.

BACKGROUND OF THE INVENTION

TGF-β is part of a superfamily of over 30 ligands that regulate several physiological processes, including cell proliferation, migration and differentiation. Perturbation of their levels and/or signaling gives rise to significant pathological effects. For instance, TGF-β and activin ligands play critical pathogenic roles in many diseases including cancer (Hawinkels & Ten Dijke, 2011; Massague et al, 2000; Rodgarkia-Dara et al, 2006). TGF-β, in particular, is considered as a critical regulator of tumor progression and is overexpressed by most tumor types. It favors tumorigenesis in part by inducing an epithelial-mesenchymal transition (EMT) in the epithelial tumor cells, leading to aggressive metastasis (Thiery et al, 2009). TGF-β also promotes tumorigenesis by acting as a powerful suppressor of the immune response in the tumor microenvironment (Li et al, 2006). In fact, TGF-β is recognized as one of the most potent immunosuppressive factors present in the tumor microenvironment. TGF-β interferes with the differentiation, proliferation and survival of many immune cell types, including dendritic cells, macrophages, NK cells, neutrophils, B-cells and T-cells; thus, it modulates both innate and adaptive immunity (Santarpia et al, 2015; Yang et al, 2010). The importance of TGF-beta in the tumor microenvironment is highlighted by evidence showing that, in several tumor types (including melanoma, lung, pancreatic, colorectal, hepatic and breast), elevated levels of TGF-β ligand are correlated with disease progression and recurrence, metastasis, and mortality. Hence, significant effort has been invested in devising anti-tumor therapeutic approaches that involve TGF-β inhibition (Arteaga, 2006; Mourskaia et al, 2007; Wojtowicz-Praga, 2003).

One approach to developing therapeutic agents that inhibit TGF-β function has been to use antibodies or soluble decoy receptors (also termed receptor ectodomain (ED)-based ligand traps) to bind and sequester ligand, thereby blocking access of ligand to its normal cell surface receptors (Zwaagstra et al, 2012). In general, receptor ED-based traps are a class of therapeutic agents that are able to sequester a wide range of ligands and that can be optimized using protein engineering approaches (Economides et al, 2003; Holash et al, 2002; Jin et al, 2009).

Previously, a novel protein engineering design strategy was used to generate single-chain, bivalent traps that are

able to potently neutralize members of the TGF-β superfamily of ligands due to avidity effects (Zwaagstra et al, 2012) [WO 2008/113185; WO 2010/031168]. In this case, bivalency was achieved via covalent linkage of two TβRII ectodomains using portions of the intrinsically disordered regions (IDR) that flank the structured, ligand-binding domain of TβRII-ED. One example of these single-chain bivalent traps, T22d35, exhibited TGF-β neutralization potencies ~100-fold higher than the monovalent non-engineered TβRII ectodomain, though it did not neutralize the TGF-β2 isoform and had a relatively short circulating half-life.

While research to date indicates that single-chain TGF-β traps have promising therapeutic potential, their circulating half-lives and manufacturability present challenges to the commercial application.

SUMMARY OF THE INVENTION

The present invention relates to TGF-β superfamily receptor ectodomain fusion molecules and uses thereof. More specifically, the present invention relates to TGF-β superfamily receptor ectodomain fusion molecules and their use in TGF-β superfamily ligand neutralization.

In some aspects, the invention relates to TGF-β superfamily receptor ectodomain-based polypeptides that are similar to typical Fc fusions in design, in that the ectodomain is fused to a dimeric antibody constant domain. In particular, with respect to the present polypeptides, the Fc portion occupies the N-terminal position. Fc fusions in the prior art typically provide the Fc portion at the C-terminal end of the fusion. As will be evident from the results presented herein, this difference in orientation provides a number of significant advantages.

In other aspects, the present polypeptides incorporate at least two TGF-β superfamily receptor ectodomains that are linked in tandem to the C-terminus of an antibody constant domain.

Thus, there is provided a polypeptide construct comprising: a first portion comprising the second constant domain (C_{H2}) and/or third constant domain (C_{H3}) of an antibody heavy chain, and a second portion comprising at least two TGF-β superfamily receptor ectodomains (TβSR-ED) linked in tandem; wherein the N-terminus of the second portion is linked to the C-terminus of the first portion.

There is also provided a polypeptide construct comprising: a first portion comprising the second constant domain (CH2) and/or third constant domain (CH3) of an antibody heavy chain, and a second portion comprising at least one TGF-β superfamily receptor ectodomains (TβSR-ED), wherein the N-terminus of the second portion is linked to the C-terminus of the first portion, and further wherein the first portion does not further comprise an antibody that binds to an antigen that is PD-L1, EGFR1, Her-2, CD4, CD6, CD20, CD25, MUC-1, IL-2, IL-6, or CTLA-4.

There is provided a polypeptide construct comprising: a first portion comprising the second constant domain (C_{H2}) and/or third constant domain (C_{H3}) of an antibody heavy chain, and a second portion comprising at least one TGF-β superfamily receptor ectodomain (TβSR-ED), wherein the N-terminus of the second portion is directly fused to the C-terminus of the first portion.

In an embodiment, there is provided a polypeptide construct comprising a first portion comprising the second constant domain (C_{H2}) and/or third constant domain (C_{H3}) of an antibody heavy chain, and a second portion comprising at least one TGF-β superfamily receptor ectodomain (TβSR-

ED), wherein the N-terminus of the second portion is linked to the C-terminus of the first portion, and wherein the polypeptide construct neutralizes TGF-β with at least 100-fold more potency than the TβSR-ED alone.

In a preferred embodiment, the second portion comprises one, two, or multiple TGF-β superfamily receptor ectodomain (TβSR-ED). In a preferred embodiment, the TβSR-ED is a TGF-β receptor type II ectodomain (TβR-II-ED). In a preferred embodiment, the TβSR-ED comprises a sequence selected from the group consisting of SEQ ID NO:35, SEQ ID NO:69, SEQ ID NO:75, SEQ ID NO:81, and a sequence substantially identical thereto.

The second portion may comprise a sequence selected from the group consisting of SEQ ID NO:43-SEQ ID NO:51, SEQ ID NO:61-SEQ ID NO:68, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:88, and a sequence substantially identical thereto.

In a preferred embodiment, the first portion of a polypeptide construct of the present invention further comprises a C_{H1}, a C_{H1} and V_H, or C_{H1} and scFv.

There is provided a polypeptide construct of the present invention wherein the antibody heavy chain is of human origin. In a preferred embodiment, the antibody heavy chain is selected from the group consisting of a human IgG1, IgG2, IgG3, or IgG4 heavy chain. More preferably, the antibody heavy chain is a human IgG1.

In accordance with the present invention, the polypeptide construct shows longer in vivo half-life compared to the half-life of the second portion alone.

There is provided a polypeptide construct of the present invention, wherein the polypeptide construct is a single chain polypeptide.

In an embodiment, the polypeptide construct forms a dimeric polypeptide. In another embodiment, the polypeptide construct is heterodimeric.

There is provided a polypeptide construct selected from the group consisting of any one of SEQ ID NO:91 to SEQ ID NO:120, and a sequence substantially identical thereto.

There is provided a polypeptide construct according to the present invention, wherein the construct comprises an antibody, antigen binding fragment thereof, or a targeting moiety. In a preferred embodiment, the antibody, the antigen binding fragment, or the targeting moiety is at the N-terminus of the first portion.

In a preferred embodiment, the antigen binding fragment may be selected from the group consisting of a Fv, scFv, Fab, or sdAb. In a preferred embodiment, the antigen binding fragment binds to any antigen, provided that it is not PD-L1, EGFR1, Her-2, CD4, CD6, CD20, CD25, MUC-1, IL-2, IL-6, or CTLA-4.

In a preferred embodiment, a polypeptide construct of the present invention comprises an antibody selected from the group consisting of Cetuximab, Avastin, Herceptin, Synagis, and FC5. In a preferred embodiment, the antibody is Cetuximab.

In a preferred embodiment, a polypeptide construct of the present invention comprises a targeting moiety, wherein the targeting moiety comprises a poly-aspartate sequence motif for bone targeting. In a preferred embodiment, the targeting moiety comprises D10.

There is provided a polypeptide construct according to the present invention wherein the construct is a dimeric polypeptide; wherein the dimeric polypeptide comprises: a first single chain polypeptide comprising a first portion comprising the second constant domain (C_{H2}) and third constant domain (C_{H3}) of an antibody heavy chain, and a heavy chain variable region of a given antibody; a second portion comprising one or more TGF-β superfamily receptor ectodomains (TβSR-ED), wherein the N-terminus of the second portion is linked to the C-terminus of the first portion, and a second single chain polypeptide comprising a first portion comprising the second constant domain (C_{H2}) and third constant domain (C_{H3}) of an antibody heavy chain, and a light chain variable region of said given antibody; a second portion comprising one or more TGF-β superfamily receptor ectodomain (TβSR-ED) which is the same or different from the ectodomain(s) in the first polypeptide, wherein the N-terminus of the second portion is linked to the C-terminus of the first portion.

There is also provided a nucleic acid molecule encoding the polypeptide construct of the present invention. There is also provided a vector comprising the nucleic acid molecule of claim the present invention.

There is also provided a composition comprising one or more than one independently selected polypeptide construct of the present invention and a pharmaceutically-acceptable carrier, diluent, or excipient.

There is also provided a transgenic cellular host comprising the nucleic acid molecule or a vector of the present invention. The transgenic cellular host further comprising a second nucleic acid molecule or a second vector encoding a second polypeptide construct different from the first polypeptide construct.

There is also provided the use of a polypeptide construct according to the present invention for treatment of a medical condition, disease or disorder; wherein the medical condition, disease or disorder comprises, but is not limited to, cancer, ocular diseases, fibrotic diseases, or genetic disorders of connective tissue.

In a preferred embodiment, there therefore provided a polypeptide construct comprising:

- a first portion comprising the second constant domain (CH2) and/or third constant domain (CH3) of an antibody heavy chain, and
- a second portion comprising at least two TGF-β superfamily receptor ectodomains (TβSR-ED),
- wherein the N-terminus of the second portion is linked to the C-terminus of the first portion.

The antibody constant domain can further comprise, either linked thereto or formed integrally therewith, a binding agent such as a full size antibody, a ligand or any other protein of interest. In the alternative, the antibody constant domain comprises only the CH2 and/or CH3 regions, and not a full size antibody. In these and other types of constructs, the CH2 and/or CH3 region can be altered by deleting or substituting amino acids including one or more of the cysteines that provide cross-linking when the present constructs are provided as dimeric constructs.

In other aspects of the present invention, there is provided a polypeptide construct that incorporates one or more such ectodomains. When the constructs comprise only one ectodomain linked to the antibody constant domain, then the construct is further characterized by at least one of the following: (1) when the constant domain further comprises a full sized antibody, that antibody does not bind effectively to PD-L1 or to an immunoregulatory antigen selected, (2) the constant domain comprises only the CH2 and/or CH3 regions, (3) the constant domain comprises an amino acid alteration relative to a wild type counterpart, such as a cysteine residue alteration; and (4) the first portion is linked to the second portion directly and without intervening amino acids.

In another of its aspects, the present invention provides a polypeptide construct comprising

a first portion comprising the second constant domain (C_{H2}) and/or third constant domain (C_{H3}) of an antibody heavy chain, and

a second portion comprising at least one TGF-β superfamily receptor ectodomain (TβSR-ED), wherein

the N-terminus of the second portion is linked to the C-terminus of the first portion. These polypeptide constructs can neutralize TGF-β, and with at least 100-fold more potency than the TβSR-ED alone.

The second portion of the polypeptide construct of the present invention may comprise one or two or more TβSR-ED. In a preferred embodiment the construct comprises two or more independently selected ectodomains linked in tandem and to the C-terminus of the constant domain. The TβSR-ED may be selected from the group consisting of a TGF-β receptor type II ectodomain (TβRII-ED), a bone morphogenetic protein receptor type Ia ectodomain (BMPR-ED), an activin receptor type IIa ectodomain (ActRIIa-ED), and an activin receptor type IIb ectodomain (ActRII-ED). In another preferred embodiment, the ectodomain is a TβR-II ectodomain.

In the polypeptide construct described herein, the first portion further may comprise a C_{H1}, a C_{H1} and V_H, or a C_{H1} and scFv. It may constitute an Fc region, an antibody, or any ligand binding agent or moiety.

The polypeptide construct of the present invention may comprise a C_{H2} and C_{H3} from an antibody heavy chain that is of human or mouse origin. For example, and without wishing to be limiting, the antibody heavy chain may be selected from the group consisting of a human IgG1, IgG2, IgG3, or IgG4 heavy chain. In embodiments, the constant domain in the constructs is CH2 per se, or CH3 per se or CH2-CH3.

The polypeptide construct described herein may show longer in vivo half-life compared to the half-life of TβSR-ED alone.

In one example, the polypeptide construct of the present invention may be a single chain polypeptide. The polypeptide construct as described herein may also form a dimeric polypeptide. This dimeric polypeptide may be heterodimeric.

The present invention further provides a polypeptide construct comprising

a first portion comprising the second constant domain (C_{H2}) and/or third constant domain (C_{H3}) of an antibody heavy chain, and

a second portion comprising at least one TGF-β superfamily receptor ectodomain (TβSR-ED),

wherein the N-terminus of the second portion is linked to the C-terminus of the first portion; additionally, in the construct as just described, the first portion is not derived from certain antibodies discussed infra.

The present invention also provides a polypeptide construct, comprising:

a first single chain polypeptide comprising a first portion comprising the second constant domain (C_{H2}) and/or third constant domain (C_{H3}) of an antibody heavy chain, and a heavy chain variable region of a given antibody; and a second portion comprising one or more TGF-β superfamily receptor ectodomains (TβSR-ED),

wherein the N-terminus of the second portion is linked to the C-terminus of the first portion, and

a second single chain polypeptide comprising a first portion comprising the second constant domain (C_{H2}) and/or third constant domain (C_{H3}) of an antibody heavy chain, and a light chain variable region of said given antibody; and a second portion comprising one or more TGF-β superfamily receptor ectodomain (TβSR-ED) which is the same or different from the ectodomain(s) in the first polypeptide, wherein the N-terminus of the second portion is linked to the C-terminus of the first portion.

In alternative constructs of the present invention, the polypeptide construct comprises an antibody Fc fragment linked at the C-terminus of each heavy chain to at least one TGF-β superfamily receptor ectodomain (TβSR-ED), as described above. In embodiments the receptor ectodomain portion comprises two independently selected ectodomains that are linked in tandem, i.e., in a linear manner. In some embodiments, the ectodomains are the same in sequence, or least the same with respect to their target ligand. The construct may further comprise a binding fragment or moiety at the N-terminus of the Fc; the binding fragment may be selected from the group consisting of a Fv, scFv, Fab, or sdAb, or any other binding moiety such as a motif for bone targeting, also as described above. In the polypeptide constructs as described above, the TGF-β receptor ectodomain does not interfere in the native function or specificity of the binding fragment.

The present invention also provides a nucleic acid molecule encoding the polypeptide constructs as described herein. A vector comprising the nucleic acid molecule just described is also encompassed by the invention. The invention also includes a transgenic cellular host comprising the nucleic acid molecule or a vector as described herein; the cellular host may further include a second nucleic acid molecule or a second vector encoding a second polypeptide construct different from the first polypeptide construct. Systems used to produce the present polypeptides can be secretion systems, particularly in the case where dimerization through disulfide bridges is required, and the expression polynucleotides thus encode secretion signals that are cleaved by the host upon secretion into the culturing medium.

Compositions comprising one or more than one independently selected polypeptide construct described herein and a pharmaceutically-acceptable carrier, diluent, or excipient are also encompassed by the present invention.

Additional aspects and advantages of the present invention will be apparent in view of the following description. The detailed descriptions and examples, while indicating preferred embodiments of the invention, are given by way of illustration only, as various changes and modifications within the scope of the invention will become apparent to those skilled in the art in light of the teachings of this invention.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other features of the invention will now be described by way of example, with reference to the appended drawings, wherein:

FIG. **1**A is a schematic diagram showing TGF-β Type II receptor ectodomain (TβRII-ED)-based molecules T2m and T22d35 along with their sequences (SEQ ID NO:43 and 46, respectively). Natural linker sequences (SEQ ID NO:36, 39 and 40) are underlined and depicted as dark grey lines; the sequence of the TβR-II-ED structured domain (SEQ ID NO:35) is shown in bold, and the domain labeled and depicted in dark grey; the site of the fusion of natural linkers is depicted by a slash. FIGS. **1**B-**1**D are schematic diagrams of IgG Fc-based scaffolds: an IgG Fc region (FIG. **1**B), a

V_HH-IgG Fc (comprising a V_HH single domain antibody fused to the N-terminus of an Fc region; FIG. 1C), and a full-size antibody (FIG. 1D).

FIGS. 2A-2G are schematic representations of TGF-β superfamily receptor-ectodomain-based fusion constructs of the present invention. (FIG. 2A) represents constructs in which T22d35 (dark grey) is fused to the C-terminus of IgG Fc regions (IgG isoforms 1, 2, 3 or 4) with no Fab or other functional binding moiety at the N-terminus (Fc-T22d35, FIG. 2A), (FIG. 2D) represents constructs in which T22d35 (dark grey) is fused to the C-terminus of the IgG Fc region of full-size antibodies with heavy and light chain Fabs (FSA-T22d35, FIG. 2D), (FIG. 2E) represents constructs in which T22d35 (dark grey) is fused to the C-terminus of IgG Fc regions that have a non-Fab binding/localization moiety at the N-terminus, such as the variable region of a camelid V_HH antibody (V_HH-Fc-T22d35) or a deca-aspartate motif for bone targeting (D10-Fc-T22d35). Similarly, (FIG. 2B), (FIG. 2C) and (FIG. 2F) and (FIG. 2G) represent constructs in which T2m (the TGF-β Type II receptor ectodomain, TβRII-ED—dark grey) is fused at the N-terminus of an IgG Fc (T2m-Fc, FIG. 2B) or the C-terminus of IgG Fc regions with no Fab or other functional binding moiety at the N-terminus (Fc-T2m, FIG. 2C), or the C-terminus of full-size antibodies with heavy and light chain Fabs (FSA-T2m, FIG. 2F), or the C-terminus of IgG Fc regions that have a non-Fab binding/localization moiety at the N-terminus, such as the variable region of a camelid V_HH antibody (V_HH-Fc-T2m, FIG. 2G) or a deca-aspartate motif for bone targeting (D10-Fc-T2m).

FIGS. 3A-3L presents (ProtA)-affinity column elution profiles, size exclusion (SEC) purification profiles, SDS-PAGE gels, and UPLC-SEC profiles of representatives of constructs type C (FIG. 2C) and D (FIG. 2D) in FIGS. 2A-2G. FIG. 3A is a (ProtA)-affinity column elution profile for T22d35 fused to the Cetuximab FSA (Cet-T22d35—a representative of construct D (FIG. 2D) in FIGS. 2A-2G). FIG. 3B is the size exclusion (SEC) purification profile of the Cet-T22d35. FIG. 3C show 4-15% SDS-PAGE gels of ProtA-purified Cet-T22d35 under reducing (left panel) and non-reducing (right panel) conditions (CetHC-T22d35, Cetuximab heavy chain fused to T22d35; CetLC, Cetuximab light chain). Lanes 1 are the pooled Prot-A eluted fractions, while lanes 2 are the pooled SEC fractions. FIG. 3D shows the UPLC-SEC profile of ProtA-purified Cet-T22d35. FIG. 3E shows the (ProtA)-affinity column elution profile for hIgG1 FcΔK(C)-T2m (a construct with T2m fused to an Fc region with no functional binding moiety at the N-terminus; a representative of construct D (FIG. 2D) in FIGS. 2A-2G). FIGS. 3F, 3G, and 3H show the UPLC-SEC profile before SEC (FIG. 3F), the UPLC-SEC profile after SEC (FIG. 3G) and the SDS-PAGE (NR & R) (FIG. 3H) of hIgG1FcΔK (C)-T2m. FIGS. 3I, 3K and 3L show the SEC profile before purification and UPLC-SEC profile after SEC purification for Fc-T2m, Fc-T22d35 and hIgG1FcΔK(C)-T22d35, respectively. FIG. 3J shows the UPLC-SEC profile for hIgG2FcΔK(CC)-Tm.

FIG. 4A shows graphs depicting the efficient inhibition of TGF-β1 (top panel), TGF-β3 (middle panel) and TGF-β2 (bottom panel) signaling in Mv1Lu luciferase reporter cells by Cet-T2m (a representative of construct F (FIG. 2F) in FIGS. 2A-2G) and Cet-T22d35 (a representative of construct D (FIG. 2D) in FIGS. 2A-2G), compared to the significantly lower inhibition potency of non-Fc-fused T22d35.

FIG. 4B shows graphs and a summary table depicting the efficient inhibition of TGF-β1 signaling in an A549/IL-11 cell-based assay by several representatives of FSA-T22d35 constructs (Type D construct (FIG. 2D) from FIGS. 2A-2G), compared to the lower inhibition potency of Fc-T2m (Type C construct (FIG. 2C)) and non-Fc-fused T22d35.

FIG. 4C shows graphs and a summary table depicting the efficient inhibition of TGF-β1 signaling in an A549/IL-11 release cell-based assay by several representatives of "headless"-T2m constructs (Type C construct (FIG. 2C) from FIGS. 2A-2G), compared to the lower inhibition potency of non-Fc-fused T22d35.

FIG. 4D is a graph showing competitive SPR analysis of binding of Cetuximab-fusion constructs to TGF-β isoforms in solution, compared to T22d35.

FIG. 5A is a SDS-PAGE gel showing the inhibition of EGFR phosphorylation in A549 cells by Cetuximab-fusion constructs. FIG. 5B is a graph showing Cet-T22d35 (triangles) cytotoxicity in MDA-MB-468 and HaCat cells compared to Cetuximab (circles) and T22d35 (squares).

FIG. 6 is a bar graph showing the apparent permeability coefficient (P_{app}) values, as a measure of transport of FC5-Fc, FCS-Fc-fusion constructs, T22d35, and T2m across a human brain endothelial cell barrier in vitro, relative to a non-transporting V_HH control (A20.1).

FIGS. 7A-7D demonstrate the Cet-T22d35 inhibition of EGF+TGF-β1 induced EMT in A549 cells. FIG. 7A shows pictures of cultured A549 cells showing their morphologies before treatment (left panel A) and after treatment with EGF+TGF-β1 (right panel B). FIG. 7B shows a western blot of whole cell lysates of A549 cells treated with EGF+TGF-β1 in the presence or absence of various concentrations of Cetuximab (Cetux), Cet-T22d35 or T22d35, probed for the epithelial marker E-Cadherin, while FIG. 7C is the densitometer quantification of the E-cadherin bands in the Western blot. Results show that Cet-T22d35 is much more potent than T22d35 alone or Cetuximab alone in upregulating E-cadherin, i.e. blocking EMT. FIG. 7D shows the inhibition of EGF+TGF-β-induced EMT by Cetuximab (Cetux), Cet-T22d35, T22d35 or Cet-T22d35 plus T22d35 as measured by flow cytometry detection of the epithelial E-Cadherin (top panel) and mesenchymal N-Cadherin (bottom panel) markers.

FIG. 8A represents the pharmacokinetic (PK) profile of Cet-T22d35 in the serum collected from BALB/C mice that were injected with a single dose of Cet-T22d35. The fusion construct appears to be cleaved in vivo; the terminal half-life of the T22d35 portion of the construct was determined to be 45.8 hours, while the terminal half-life of the Cetuximab portion of the construct was determined to be 262.5 hours. FIG. 8B represents the PK profiles and data table (serum half-lives in bold) for constructs in which the lysine at the C-terminus of the Fc region was removed, i.e. is not present at the fusion joint between the Fc region and T2m (CetΔK-T2m, hIgG1 FcΔK(SS)-T2m, hIgG1FcΔK(AC)-T2m, and hIg2GFcΔK(SS)-T2m). The data demonstrate that the removal of the lysine prevents cleavage of the constructs in vivo.

FIGS. 9A, 9B and 9C present graphs showing the effect of "headless" Fc-T2m constructs (representatives of construct C (FIG. 2C) in FIGS. 2A-2G) and a FSA-T2m construct (a representative of construct F (FIG. 2F) in FIGS. 2A-2G) on tumor growth and T-cell function in an immune-competent syngeneic triple negative breast cancer (4T1) model (for comparison, the effects of the 1D11 antibody and non-Fc-fused T22d35 are also shown). The results demonstrate the improved efficacy on T-cell function of two headless-T2m constructs relative to the FSA-T2m construct, and relative to 1D11 and non-Fc-fused T22d35.

FIGS. **10**A-**10**D show data illustrating enhanced bone localization of two constructs containing a deca-aspartate motif for bone targeting at the N-terminus of the Fc region (D10-hIgG1FcΔK(CC)-T2m (SEQ ID NO:136) and D10-GSL-hIgG1FcΔK(CC)-T2m (SEQ ID NO:137)—representatives of construct G (FIG. **2**G) in FIGS. **2**A-**2**G). FIGS. **10**A and **10**B show results from an A549/IL-11 release cell-based assay demonstrating that the addition of D10 at the N-terminus did not affect TGF-β neutralization potency. FIGS. **10**C and **10**D show images demonstrating significant enhancement of the accumulation of the D10-containing constructs in bones relative to a construct without D10.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to TGF-β superfamily receptor ectodomain fusion molecules and uses thereof. More specifically, the present invention relates to TGF-β superfamily receptor ectodomain fusion molecules and their use in TGF-β superfamily ligand neutralization.

The present invention provides polypeptide constructs, comprising

- a first portion comprising the second constant domain (C_{H2}) and/or third constant domain (C_{H3}) of an antibody heavy chain, and
- a second portion comprising at least one TGF-β superfamily receptor ectodomain (TβSR-ED),

wherein the N-terminus of the second portion (ectodomain) is linked to the C-terminus of the first portion (Fc region), and wherein the polypeptide construct neutralizes TGF-β with at least 100-fold more potency than the TβSR-ED alone. The polypeptide construct referred to herein is a synthetic polypeptide produced via protein engineering. It comprises two protein "portions" (or "parts") that are linked to form the chimeric polypeptide construct. When the polypeptide construct is expressed, two polypeptide chains dimerize, such that the C_{H2} and C_{HH} domains form an antibody Fc region.

In specific embodiments of the present invention, descriptions of which are elaborated further herein, there are provided polypeptide constructs in which TGF-β superfamily receptor-ectodomains were fused to IgG Fc regions. Specifically, the T2m (single ectodomain) or T22d35 (double ectodomain) moieties were linked (fused) to the C-terminal end of the Fc region. It was observed that fusion constructs of this type have advantages relative to several other versions of receptor-ectodomain based molecules, including non-Fc fused monovalent or multivalent TGF-β receptor ectodomain constructs (such as T2m and T22d35) and constructs in which a receptor ectodomain is fused to the N-terminus of an Fc region. In particular, the constructs have improved manufacturability due to the presence of the Fc region (for example, purification can be accomplished using protein A chromatography). The Fc region also allows for improved circulating half-lives. Importantly, the present constructs have substantially higher TGF-β neutralization potencies compared to T2m and T22d35 alone or to constructs where a receptor ectodomain is fused to the N-terminus of an Fc region. Thus, an advantage of the present invention is unexpected high potency TGF-β superfamily ligand neutralization, including some degree of neutralization of TGF-β2, which was not observed for the non-Fc fused constructs T2m and T22d35. Finally, constructs in accordance with embodiments of the present invention, that is where the ectodomain(s) is/are fused to the C-terminus of an Fc region of an antibody, allows for preservation of the structure and function of the natural N-terminal regions/domains of an antibody; as such, antigen binding to the antibody CDR regions is not perturbed. This leads to the generation of a bifunctional construct able to interact with the target of the antibody while interacting with, and neutralizing, members of the TGF-β superfamily of ligands.

The invention relates not only to bifunctional constructs, but also to constructs that are monofunctional, and comprise an Fc region that consists only of the CH2 and/or CH3 regions of an antibody constant region. Preferably, the G1, G2 or G4 subclasses are used, and particularly G1 as well as G2. These constructs are monofunctional in the sense that the constant region itself has no particular activity, other than to act as a structure through which dimers of the polypeptide constructs can form. These minimal constant regions can also be altered to provide some benefit, by incorporating the corresponding hinge regions (SEQ ID NO:5-8) and optionally changing the cysteine residue composition. Thus, some or all of the cysteine residues involved in bridging the two Fc fragments or naturally used to bridge between the heavy and light chains of a full-length antibody can be replaced or deleted. These cysteine residues are seen in hinge sequences listed in SEQ ID NO:5-8. First, not all of the naturally-occurring inter-hinge disulfide bonds need to be formed for the Fc homodimerization to occur, while noting that the stability of the Fc homodimer may depend on the number of intermolecular disulphide bridges. Secondly and perhaps more importantly, the presence of hinge-region cysteine residues may become problematic when the Fc region lacks its N-terminal Fab fragment (i.e., is a headless Fc) as in the case of some polypeptide constructs of the present invention. This leads to untethering and exposure of these hinge-region cysteines, and in turn that may result in complex mixtures of high-order polymeric chains, which creates manufacturability issues in addition to potentially diminishing the intended biological activity and efficacy. Because it is practically impossible to predict the outcome of varying the number of inter-hinge disulphide bridges for the "headless" polypeptide constructs of the present invention, we generated a systematic array of N-terminal Fc variants for all four human IgG isotypes either by a deletion approach (in which hinge-region cysteine residues are progressively eliminated by N-terminal truncations) or by a mutagenesis approach (in which hinge-region cysteine residues are progressively mutated to serine from the N-terminus of the hinge region). Non-limiting examples of such N-terminal variants of headless Fc regions are listed in SEQ ID NO:9-34.

In the present disclosure, an "antibody", also referred to in the art as "immunoglobulin" (Ig), refers to a protein constructed from paired heavy and light polypeptide chains; various Ig isotypes exist, including IgA, IgD, IgE, IgG, and IgM. The structure of an antibody and of each of the domains is well-established and familiar to those of skill in the art, though is summarized herein. When an antibody is correctly folded, each chain folds into a number of distinct globular domains joined by more linear polypeptide sequences; the immunoglobulin light chain folds into a variable (V_L) and a constant (C_L) domain, while the heavy chain folds into a variable (V_H) and three constant (C_H, C_{H2}, C_{H3}) domains. Once paired, interaction of the heavy and light chain variable domains (V_H and V_L) and first constant domain (C_L and C_{H1}) results in the formation of a Fab (Fragment, antigen-binding) containing the binding region (Fv); interaction of two heavy chains results in pairing of C_{H2} and C_{H3} domains, leading to the formation of a Fc

(Fragment, crystallisable). Characteristics described herein for the C_{H2} and C_{H3} domains also apply to the Fc.

While the light and heavy chain variable regions show significant sequence diversity between antibodies, the constant regions show less sequence diversity and are responsible for binding a number of natural proteins to elicit important biochemical events. Specifically, and without wishing to be limiting, the Fc fragment binds to endogenous Fc receptors on the surface of lymphocytes.

The C_{H2} and C_{H3} domains of the first portion may be of any isotype, including one selected from the group consisting of IgA, IgD, IgE, and IgG. The C_{H2} and C_{H3} domains may also be from any suitable source. For example and without wishing to be limiting, the C_{H2} and C_{H3} domains may originate from a human, mouse and other rodents like rats and degu, rabbit, monkey, or other mammalian source. In one example, the C_{H2} and C_{H3} domains may be of the IgG isotype; in another example, the C_{H2} and C_{H3} domains are from human.

In a specific, non-limiting example, the C_{H2} and C_{H3} domains of the first portion may be of an isotype or comprise a sequence selected from the group consisting of:

```
a human IgG1, for example but not limited to SEQ
ID NO: 1
(APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY

VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA

LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD

IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC

SVMHEALHNHYTQKSLSLSPGK) as comprised in P01857 of

the UniProtKB/Swiss-Prot database;

a human IgG2, for example but not limited to SEQ
ID NO: 2
(APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYV

DGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGL

PAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI

SVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCS

VMHEALHNHYTQKSLSLSPGK), as comprised in P01859 of

the UniProtKB/Swiss-Prot database;

a human IgG3, for example but not limited to SEQ
ID NO: 3
(APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFKWY

VDGVEVHNAKTKPREEQYNSTFRVVSVLTVLHQDWLNGKEYKCKVSNKA

LPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD

IAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSC

SVMHEALHNRFTQKSLSLSPGK), as comprised in P01860

of the UniProtKB/Swiss-Prot database;

a human IgG4, for example but not limited to SEQ
ID NO: 4
(APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY

VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG

LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD
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IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC

SVMHEALHNHYTQKSLSLSLGK), as comprised in P01861

of the UniProtKB/Swiss-Prot database;
```

and

a sequence substantially identical to any of the sequences listed above.

In the protein constructs of the present invention, the first portion may further comprise a sequence corresponding to the hinge region at the N-terminus of the C_{H2} domain. For example, the first portion may further comprise a sequence selected from the group consisting of:

```
                                        (SEQ ID NO: 5)
EPKSCDKTHTCPPCP for human IgG1;

                                        (SEQ ID NO: 6)
ERKCCVECPPCP for human IgG2;

                                        (SEQ ID NO: 7)
ELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEP
KSCDTPPPCPRCP for human IgG3;

                                        (SEQ ID NO: 8)
ESKYGPPCPSCP for human IgG4;
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and a sequence substantially identical to any of the sequences listed above.

Thus, the first portion of the polypeptide construct of the present invention consists of naturally fused Fc and hinge regions for the various IgG isoforms and in embodiments is selected from the group consisting of SEQ ID NO:1-4 for the Fc region and SEQ ID NO:5-8 for the hinge region.

In specific embodiments, the first portion of the polypeptide construct of the present invention is selected from a group of sequences displaying variation in the N-terminal sequence as exemplified by SEQ ID NO:9-34. These differ in the number of cysteine residues retained from the hinge region as a means to modulating the degree of Fc-region dimerization and hence impacting on both efficacy and manufacturability. Thus, in embodiments, the polypeptide construct comprises a variation in the constant domain, wherein at least one cysteine residue involved in cross-linking is deleted or substituted. Suitable substitutions include serine or alanine, and preferably by serine. A substantially identical sequence may comprise one or more conservative amino acid mutations that still provide for proper folding upon secretion into the culturing medium. It is known in the art that one or more conservative amino acid mutations to a reference sequence may yield a mutant peptide with no substantial change in physiological, chemical, physico-chemical or functional properties compared to the reference sequence; in such a case, the reference and mutant sequences would be considered "substantially identical" polypeptides. A conservative amino acid substitution is defined herein as the substitution of an amino acid residue for another amino acid residue with similar chemical properties (e.g. size, charge, or polarity). These conservative amino acid mutations may be made to the framework regions while maintaining the overall structure of the constant domains; thus the function of the Fc is maintained.

In a non-limiting example, a conservative mutation may be an amino acid substitution. Such a conservative amino acid substitution may substitute a basic, neutral, hydrophobic, or acidic amino acid for another of the same group. By the term "basic amino acid" it is meant hydrophilic amino acids having a side chain pK value of greater than 7, which are typically positively charged at physiological pH. Basic

amino acids include histidine (His or H), arginine (Arg or R), and lysine (Lys or K). By the term "neutral amino acid" (also "polar amino acid"), it is meant hydrophilic amino acids having a side chain that is uncharged at physiological pH, but which has at least one bond in which the pair of electrons shared in common by two atoms is held more closely by one of the atoms. Polar amino acids include serine (Ser or S), threonine (Thr or T), cysteine (Cys or C), tyrosine (Tyr or Y), asparagine (Asn or N), and glutamine (Gln or Q). The term "hydrophobic amino acid" (also "non-polar amino acid") is meant to include amino acids exhibiting a hydrophobicity of greater than zero according to the normalized consensus hydrophobicity scale of (Eisenberg et al, 1984). Hydrophobic amino acids include proline (Pro or P), isoleucine (Ile or I), phenylalanine (Phe or F), valine (Val or V), leucine (Leu or L), tryptophan (Trp or W), methionine (Met or M), alanine (Ala or A), and glycine (Gly or G).

"Acidic amino acid" refers to hydrophilic amino acids having a side chain pK value of less than 7, which are typically negatively charged at physiological pH. Acidic amino acids include glutamate (Glu or E), and aspartate (Asp or D).

In another non-limiting example, a conservative mutation in the C_{H2} and/or C_{H3} domain may be a substitution that enhances a property selected from the group consisting of the stability, half-life, or Fc properties of C_{H2} and/or C_{H3} domains or alter glycosylation of the C_{H2} and/or C_{H3} domain. For example, and without wishing to be limiting in any manner, the mutation may be an alteration at position 228 (EU numbering, 241 according to Kabat) where the serine is substituted by a proline (S228P), which stabilizes the disulfide linkage within the Fc dimer. Another alteration is the mutation at position 409 (EU numbering, 440 according to Kabat) where an arginine is substituted to a lysine for further stabilization of the Fc homodimer at the C_{H3}-domain level (Yang & Ambrogelly, 2014). Yet another alteration within the C_{H2} and/or C_{H3} domain may be a substitution of Asn297 (EU numbering, 314 according to Kabat) by glycine or alanine to alter glycosylation of the constant domain. In yet another example, the C_{H2} and/or C_{H3} domain may be altered by substitution of one or more threonine (T252L, T253S, and/or T256F; see [U.S. Pat. No. 62,777,375]) to increase half-life. Particularly useful are those alterations that enhance Fc properties while remaining silent with respect to conformation, e.g., retaining Fc receptor binding.

In yet another non-limiting example, the conservative mutations in the C_{H2} and/or C_{H3} domain may be a substitution that is naturally-occurring. Such mutations may occur in nature as minor sequence differences between species or race.

Sequence identity is used to evaluate the similarity of two sequences; it is determined by calculating the percent of residues that are the same when the two sequences are aligned for maximum correspondence between residue positions. Any known method may be used to calculate sequence identity; for example, computer software is available to calculate sequence identity. Without wishing to be limiting, sequence identity can be calculated by software such as NCBI BLAST2 service maintained by the Swiss Institute of Bioinformatics (and as found at ca.expasy.org/tools/blast/), or any other appropriate software that is known in the art.

The substantially identical sequences of the present invention may be at least 90% identical; in another example, the substantially identical sequences may have an identity selected from the group consisting of at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identical, or any percentage there between, at the amino acid level to sequences described herein. Importantly, the substantially identical sequences retain the activity, specificity, and functionality of the reference sequence. In a non-limiting embodiment, the difference in sequence identity may be due to conservative amino acid mutation(s). In a non-limiting example, the first portion of the polypeptide construct of the present invention may comprise a Fc comprising a sequence selected from the group consisting of a sequence at least 95%, 98% or 99% identical to that of the Fc described herein.

Accordingly, it will be appreciated that the first portion of a construct will include at least an antibody region that preferably provides for cross-linking of the polypeptide constructs, thereby to provide a dimeric protein. This first portion comprises at least the minimal CH2 and/or CH3 domain. That portion can be altered (i) by substituting or deleting cysteine residues from the hinge regions (SEQ ID NO:5-8) involved in crosslinking between the antibody heavy chains or between the heavy and light chains in order to potentially improve preparation homogeneity and efficacy, and/or (ii) by deleting or suitably replacing (e.g., by mutation to alanine) the terminal lysine residue 447 (EU numbering, 478 according to Kabat) of an IgG heavy chain in order to improve chemical stability of C-terminal fusions to enzymatic proteolysis (e.g., by several serine proteases and typically by trypsin). These changes have a positive impact on potency and/or manufacturability, as revealed herein. The first portion can also be extended to become a full Fc region, by including the CH1 domain. As a full Fc, this portion will provide normal Fc effector functions that include involvement in immune cell recruitment, ADCC, CDC and other antibody functions. Moreover, and in embodiments of the present invention, the first portion can include a complete antibody or any equivalent thereof. In certain embodiments, such as when a construct comprises just one ectodomain that is a TGF-β receptor II ectodomain, there is the proviso that the second portion is not an antibody that binds to an immune checkpoint protein such as PD-L1 (programmed death ligand 1) and is not an antibody that binds to an immunomodulating agent that counteracts immune tolerance of cancer cells, the nature and identity of which is as described in [U.S. Pat. No. 8,815,247], and is not an antibody that binds one of EGFR1, her-2, CD4, CD6, CD20, CD25, MUC-1, IL-2, IL-6, and CTLA-4.

The second portion of the polypeptide construct of the present invention comprises at least one and preferably two TGF-β superfamily receptor ectodomain/s (TβSR-ED); for example, the second portion may comprise one or two TβSR-ED. The ectodomain of the Transforming Growth Factor-β superfamily receptor (TβSR) is the N-terminal extracellular, ligand-binding portion of the receptor. Without wishing to be limiting in any manner, the TβSR ectodomain may bind a molecule selected from the group consisting of TGF-β, bone morphogenetic protein (BMP) including BMP2, BMP3, BMP4, BMPS, BMP, BMP6, BMP7, BMP8, BMP9, BMP10, BMP11, BMP12, BMP13, BMP14, an BMP15, activin including activins βA, βB and βC, growth differentiation factor (GDF-1) including GDF-3, GDF-8, GDF-9, and GDF-15, nodal, inhibin-α, anti-Mullerian hormone, Lefty-1, Lefty-2, arteman, persephin, neurturin, myostatin, or other known TGF-β superfamily ligands. For example, the TβR ectodomain may be selected from the group consisting of the human TGF-β receptor type II ectodomain (TβR-II-ED), the human TGF-β receptor type IIb (TβR-IIb) ectodomain, the human activin receptor type IIa (ActR-IIa) ectodomain, the human activin receptor type IIb (ActR-IIb) ectodomain, or the BMP type Ia (BMPR-Ia) ectodomain.

In a preferred embodiment the ectodomain binds TGF-β1 and/or TGF-β3. In another preferred embodiment, the ectodomain itself is a human TGF-β receptor type II ectodomain including particularly the TGF-β receptor type IIa (TβRIIa). In one specific, non-limiting example, the TβSR-ED is the TGF-β receptor type II ectodomain (TβRII-ED; SEQ ID NO:35).

In the second portion as described above, the TβSR ectodomain-based portion may further comprise natural linkers. Appropriate, naturally-derived linkers that can be used to fuse two ectodomains head-to-tail are known to those of skill in the art; for example, and without wishing to be limiting, suitable natural linkers are described in [WO2008/113185].

In this embodiment, the natural linker, if present, may be selected from the group consisting of

(SEQ ID NO: 36)
IPPHVQKSVNNDMIVTDNNGAVKFP;

(SEQ ID NO: 37)
IPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFP;

(SEQ ID NO: 39)
SEEYNTSNPD;

(SEQ ID NO: 40)
SEEYNTSNPDIPPHVQKSVNNDMIVTDNNGAVKFP;

(SEQ ID NO: 41)
SEEYNTSNPDIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFP;

and

a combination thereof.

In a specific, non-limiting example, the second portion of the polypeptide construct of the present invention may comprise the sequence selected from the group consisting of:

A single TGF-β Type II receptor ectodomain, such as:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 43, also referred to herein as T2m);

(SEQ ID NO: 44)
IPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD;

A TGF-β Type II receptor ectodomain "doublet", in which a TGF-β Type II receptor ectodomain is linked with another TGF-β Type II receptor ectodomain, which ectodomains can be the same or different TGF-β superfamily receptor ectodomains, such as:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDIPPHVQKSVNN

-continued

DMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 46, also referred to herein as T22d35);

(SEQ ID NO: 47)
IPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDIPPHVQKSDVEMEAQKDEIICPSCNRTAHPLRHINNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD;

and

a sequence substantially identical thereto. "Substantially identical" is as defined above.

In another specific, non-limiting example, the TGF-β receptor ectodomain is the bone morphogenetic protein receptor Ia (BMPRIa; SEQ ID NO:69). In this embodiment, the natural linker, if present, may be selected from the group consisting of

(SEQ ID NO: 70)
QNLDSMLHGTGMKSDSDQKKSENGVTLAPED;

(SEQ ID NO: 71)
PVVIGPFFDGSIR;

(SEQ ID NO: 72)
PVVIGPFFDGSIRQNLDSMLHGTGMKSDSDQKKSENGVTLAPED;

and

a combination thereof.

Thus, in a specific, non-limiting example, the second portion of the polypeptide construct of the present invention may comprise the sequence selected from the group consisting of:

(SEQ ID NO: 74)
QNLDSMLHGTGMKSDSDQKKSENGVTLAPEDTLPFLKCYCSGHCPDDAINNTCITNGHCFAIIEEDDQGETTLASGCMKYEGSDFQCKDSPKAQLRRTIECCRTNLCNQYLQPTLPPVVIGPFFDGSIRQNLDSMLHGTGMKSDSDQKKSENGVTLAPEDTLPFLKCYCSGHCPDDAINNTCITNGHCFAIIEEDDQGETTLASGCMKYEGSDFQCKDSPKAQLRRTIECCRTNLCNQYLQPTLPPVVIGPFFDGSIR;

and

a sequence substantially identical thereto. "Substantially identical" is as defined above.

In another specific, non-limiting example, the TβSR ectodomain is the activin receptor IIa (ActRIIa; SEQ ID NO:75). In this embodiment, the natural linker, if present, may be selected from the group consisting of

(SEQ ID NO: 76)
AILGRSE;

(SEQ ID NO: 77)
EMEVTQPTSNPVTPKPPYYNI;

(SEQ ID NO: 78)
EMEVTQPTSNPVTPKPPYYNIAILGRSE;

and

a combination thereof.

Thus, another specific non-limiting example of the second portion of the polypeptide construct of the present invention comprises the sequence selected from the group consisting of:

(SEQ ID NO: 80)
AILGRSETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFATWKNIS
GSIEIVKQGCWLDDINCYDRTDCVEKKDSPEVYFCCCEGNMCNEKFSYF
PEMEVTQPTSNPVTPKPPYYNIAILGRSETQECLFFNANWEKDRTNQTG
VEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKK
DSPEVYFCCCEGNMCNEKFSYFPEMEVTQPTSNPVTPKPPYYNI;

and

a sequence substantially identical thereto. "Substantially identical" is as defined above.

In another specific, non-limiting example, the TGF-β receptor ectodomain is the activin receptor IIb (ActRIIb; SEQ ID NO:81). In this embodiment, the natural linker, if present, may be selected from the group consisting of

(SEQ ID NO: 82)
SGRGEAET;

(SEQ ID NO: 83)
EAGGPEVTYEPPPTAPT;

(SEQ ID NO: 84)
EAGGPEVTYEPPPTAPTSGRGEAET;

and

a combination thereof.

Thus, another specific non-limiting example of the second portion of the polypeptide construct of the present invention comprises the sequence selected from the group consisting of:

(SEQ ID NO: 86)
SGRGEAETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSS
GTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHL
PEAGGPEVTYEPPPTAPTSGRGEAETRECIYYNANWELERTNQSGLERC
EGEQDKRLHCYASWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQ
VYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPT;

and

a sequence substantially identical thereto. "Substantially identical" is as defined above.

Thus, in various embodiments of the present invention, the present constructs have an ectodomain comprising an amino acid sequence selected from the group consisting of SEQ ID NO:35, SEQ ID NO:69, SEQ ID NO:75, SEQ ID NO:81, and a sequence substantially identical thereto. In other embodiments, the second portion comprises the entire extracellular portion of a TβSR-ED consisting of a sequence selected from the group consisting of SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:73, SEQ ID NO:79, SEQ ID NO:85, and a sequence substantially identical thereto.

The at least two ectodomain portion can have the same or different ectodomains, all belonging to the superfamily. In embodiments, the ectodomains bind the same target. In other embodiments, the ectodomains originate from the same receptor species. In other embodiments, the ectodomains are identical and thus are homomeric. In other embodiments the ectodomains are different and thus are heteromeric. In these embodiments, the ectodomain can be for instance a TβRII-ED that is type a, and another ectodomain can be a TβRII-ED that is type b. A third ectodomain could be the same as either one of these, or different still. For example, when there is more than one ectodomain in the second portion of the polypeptide construct of the present invention, the ectodomains may be all the same (homomers) or all different (heteromers), or any combination of superfamily ectodomains.

Thus, in embodiments, the second portion of the polypeptide construct of the present invention comprises a repeat of a given TβSR-ED selected from the group consisting of SEQ ID NO:46, 47, 48, 74, 80, 86, and a sequence substantially identical thereto.

In specific embodiments, the second portion of the polypeptide construct of the present invention comprises heteromeric repeats of two distinct TβSR-EDs genetically fused and selected from the group consisting of SEQ ID NO:61, 62, 63, 88, and a sequence substantially identical thereto.

In yet other embodiments, the second portion of the polypeptide construct of the present invention comprises homo-multimeric and hetero-multimeric repeats of one or more TβSR-EDs selected for instance from the group consisting of SEQ ID NO:49, 50, 51, 64, 65, 66, 67, 68, and a sequence substantially identical thereto.

In the protein construct of the present invention, the first and second portions of the polypeptide construct of the present invention are linked. By the term "linked", it is meant that the two portions are covalently bonded. The chemical bond may be achieved by chemical reaction, or may be the product of recombinant expression of the two portions in a single polypeptide chain. In one specific, non-limiting example, the C-terminus of the first portion is linked directly to the N-terminus of the second portion, that is, no additional "linker" amino acids are present between the two portions. In the case where no linker is present, that is to say direct fusion of the two portions, there will be a direct link between the N-terminus of the full ectodomain and the C-terminus of the antibody constant regions C_{H2}-C_{H3}. For example, in fusing the Fc variant SEQ ID NO:9 to the SEQ ID NO:43 via the intrinsically disordered linker with SEQ ID NO:36, which is part of the TβRII-ED (i.e., no additional "linker" amino acids added), one connects the glycine at the last position of SEQ ID NO:9 to the isoleucine at the first position of SEQ ID NO:43.

A common practice when producing fusion constructs is to introduce glycine or glycine-serine linkers (such as GGGGS, or $[G_4S]_n$) between the fused components. As taught in the above paragraph, the polypeptide fusions of the present invention can be produced by direct linkage without use of any additional amino-acid sequence except those present in the Fc portion and in the receptor ectodomain portion. One thus can refrain from utilizing foreign sequences as linkers, providing an advantage due to their potential for undesired immunogenicity and their added molecular weight. Entropic factors are also a potential

liability for glycine and glycine-serine linkers, which are highly flexible and may become partially restricted upon target binding, hence causing a loss of entropy unfavourable to binding affinity. Therefore, only the flexible, intrinsically disordered N-terminal regions of the TβSR receptor ectodomains were employed as natural linkers in embodiments of the present invention. However, the particular amino acid compositions and lengths of these intrinsically disordered linkers (e.g., SEQ ID NO:36, 37, 70, 76, 82) precluded accurate prediction of whether the resulting direct-fusion constructs will have the required geometry and favourable molecular interactions for correct binding to their intended dimeric ligands.

The first and second portions of the polypeptide construct are, in embodiments, connected by natural intrinsically disordered polypeptide linkers selected from the group consisting of SEQ ID NO:36, 37, 38, 53, 70, 76, 82, and a sequence substantially identical thereto.

In embodiments, when multiple TβSR-ED structured regions are present, these can be fused directly or they can be connected by natural intrinsically disordered polypeptide linkers between the ectodomains, such as SEQ ID NO:40, 41, 42, 55, 58, 59, 60, 72, 78, 84, 87, and a sequence substantially identical thereto.

Non-limiting examples of full-length polypeptide constructs of the present invention that comprise the two aforementioned portions are selected from the group consisting of SEQ ID NO: 91-120, and a sequence substantially identical thereto.

It is particularly important to note that, in the polypeptide constructs of the present invention, the N-terminus of the second portion is linked to the C-terminus of the first portion (see for example FIGS. **2**A, C, D, E, F, and G).

Some of the polypeptide constructs of the present invention display significantly greater potency of TGF-β neutralization compared to that of the TGF-β superfamily receptor ectodomain alone; for example, the polypeptide construct may be between at least 50-fold and 1×10^6-fold more potent. For example, the polypeptide constructs of the present invention may have a TGF-β neutralization potency selected from the group consisting of at least 50-, 75-, 100-, 150-, 200 -300-, 400-, 500-, 600, 1000 -1500-, 2000-, 3000-, 4000-, 5000-, 6000-, 7000-, 8000-, 9000, 10000-, 20000-, 30000-, 40000-, 50000-, 60000-, 70000-, 80000-, 90000-, 100000-, 150000-, 200000-, 250000-, 300000-, 350000-, 400000-, 450000-, 500000-, 550000-600000-, 650000-, 700000-, 750000-, 800000-, 850000-, 900000-, 950000, or 1000000-fold, more potent than the TβSR-ED alone, or any amount there between. In one example, the potency of the construct is at least 100-fold greater than the receptor ectodomain alone.

Additionally, when the polypeptide constructs of the present invention include a TβSR-ED that binds TGF-β, the polypeptide construct may neutralize, to varying extents, all three isotypes of TGF-β (that is, TGF-β1, TGF-β2, and TGF-β).

The polypeptide constructs of the present invention have, as assessed in cell-based assays, TGF-β neutralizing potencies that are significantly higher (100-fold or more) than those of bivalent comparator polypeptides, i.e. non-Fc-fused T22d35 and T2m-Fc. Within the series of polypeptide constructs of the present invention, those that contain two or more copies of the TβRII ectodomain fused to the C-terminus of the Fc constant region have potencies that are higher than those constructs that contain only one copy, as assessed in cell based assays. Additionally, within the series of polypeptide constructs of the present invention, if the first portion within the construct is "headless", i.e. does not contain a Fab region, the potencies of the constructs are increased by engineering (optimizing) the number of cysteines in the hinge region at the "revealed" N-terminus. Engineering of the cysteine residues at the N-termini of "headless" constructs also markedly reduces the aggregation propensity of the constructs. Lastly, within the series of polypeptide constructs of the present invention, in vivo in tumor models, cysteine optimized "headless" constructs exhibit higher anti-tumor immuno-modulatory potencies than constructs in which the first portion is a full-sized antibody.

The polypeptide construct of the present invention is expressed as a single polypeptide chain. Once expressed, the polypeptide construct of the present invention forms a dimer wherein the C_{H2} and C_{H3} domains of the respective polypeptide constructs interact to form a properly assembled Fc region such as occurs when the expressed products are secreted into the culturing medium. For example, and without wishing to be limiting, examples of dimerized polypeptide constructs of the present invention are shown in FIGS. **2**A and C-G. In one example, homodimers may be formed by identical polypeptide constructs. Alternatively, heterodimers may be formed by two different polypeptide constructs; thus, a heterodimer may be formed by two Fc region polypeptide constructs that have been engineered to induce heterodimerization and inhibit homodimerization.

The first portion of the polypeptide construct described above may further comprise, at its N-terminus, any suitable antigen-binding antibody fragment known in the art. For example, and without wishing to be limiting in any manner, the first portion of the polypeptide construct may comprise C_{H2} and C_{H3} domains and one selected from the group consisting of a single-chain Fv (scFv; a molecule consisting of V_L and V_H connected with a peptide linker) and a single-domain antibody (sdAb, a fragment composed of a single V_L or a single V_H; see for example FIG. **1**C). In other instances, the antigen-binding fragment may be formed by combining the polypeptide construct with a second polypeptide chain. For example, the first portion of the polypeptide construct may comprise C_{H2} and C_{H3} domains along with a C_{H1} and V_H domains, which when combined with a second polypeptide comprising C_L and V_L form a full-size antibody (i.e., Fc and Fab; see for example FIG. **1**D). In another example, the first portion of the polypeptide may comprise C_{H2} and C_{H3} domains along with V_H, which when combined with a second polypeptide comprising a V_L forms an Fc fused to a Fv.

The combination of constant domains and antigen-binding fragment may be naturally-occurring, or may be obtained by manipulation of a naturally-occurring antibody or by using recombinant methods. The polypeptide constructs such as those just described may require a sequence selected from the group consisting of linker sequences, disulfide bonds, hinge region sequences, and other type of covalent bond to link them to the C_{H2} and C_{H3} domains; those of skill in the art will be familiar with various suitable approaches.

In alternative constructs of the present invention, the polypeptide construct comprises an antibody Fc fragment linked at the C-terminus of each heavy chain to at least one TGF-β superfamily receptor ectodomain (TβSR-ED), as described above and as illustrated in FIG. **2**(A,D,E). The construct may further comprise an antigen-binding fragment at the N-terminus of the Fc; the antigen-binding fragment may be selected from the group consisting of a Fv, scFv, Fab, or sdAb, also as described above. In the polypeptide con-

structs as described above, the TGF-β receptor ectodomain does not interfere in the native function or specificity of the antigen-binding fragment.

The antigen-binding antibody fragment described above, when present, may be directed to any suitable antigen. In certain limited embodiments, the antigen-binding antibody or fragment does not bind to an antigen that is PD-L1, EGFR1, her-2, CD4, CD6, CD20, CD25, MUC-1, IL-2, IL-6, or CTLA-4.

The present constructs can further comprise antibody or antibody fragments that target any antigen of interest. They can also comprise the antigen itself, or any other moiety of interest that is genetically encoded. Particular embodiments herein include the EGFR antibody cetuximab and its active fragments, Avastin, Herceptin, Synagis, FC5, or a poly-aspartate bone-localization motif, such a D10, or sequence substantially identical or equivalent thereto.

The present constructs can comprise a binding protein e.g., antibody and binding fragments thereof, that inhibits a checkpoint protein which may be CTLA-4, PD1, PDL1, PDL2, PDL3, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GALS, LAGS, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, CD28, CD86, or one of the B-7 family ligands or a combination thereof.

Illustrative immune checkpoint inhibitors include Tremelimumab (CTLA-4 blocking antibody), anti-OX40, PD-LI monoclonal Antibody (Anti-B7-HI; MED14736), MK-3475 (PD-1 blocker), Nivolumab (anti-PDI antibody), CT-011 (anti-PDI antibody), BY55 monoclonal antibody, AMP224 (anti-PDLI antibody), BMS-936559 (anti-PDLI antibody), MPLDL3280A (anti-PDLI antibody), MSB0010718C (anti-PDLI antibody) and Yervoy/ipilimumab (anti-CTLA-4 checkpoint inhibitor).

Other antibodies provided by the present constructs can include rituximab, muromonab-CD3, abciximab, daclizumab, basiliximab, palivizumab, infliximab, trastuzumab, gemtuzumab ozogamicin, alemtuzumab, ibritumomab tiuxetan, adalimumab, omalizumab, tositumomab, I-131 tositumomab, efalizumab, bevacizumab, panitumumab, pertuzumab, natalizumab, etanercept, IGN101, volociximab, Anti-CD80 mAb, Anti-CD23 mAb, CAT-3888, CDP-791, eraptuzumab, MDX-010, MDX-060, MDX-070, matuzumab, CP-675,206, CAL, SGN-30, zanolimumab, adecatumumab, oregovomab, EGFR-binding antibodies cetuximab, nimotuzumab, necitumumab, panitumumab, matuzumab, and zalutumumab, as well as ABT-874, denosumab, AM 108, AMG 714, fontolizumab, daclizumab, golimumab, CNTO 1275, ocrelizumab, HuMax-CD20, belimumab, epratuzumab, MLN1202, visilizumab, tocilizumab, ocrerlizumab, certolizumab, eculizumab, pexelizumab, abciximab, ranibizimumab, mepolizumab, TNX-355, or MYO-029.

Still other antibodies that can be included in the present constructs are rituximab, zanolimumab, hA20, AME-133, HumaLYM, trastuzumab, pertuzumab, IMC-3G3, ch806, KSB-102, MR1-1, SC100, SC101, SC103, alemtuzumab, muromonab-CD3, OKT4A, ibritumomab, gemtuzumab, alefacept, abciximab, basiliximab, palivizumab, motavizumab, infliximab, adalimumab, CDP-571, etanercept, ABX-CBL, ABX-IL8, ABX-MA1 pemtumomab, Therex, AS1405, natalizumab, HuBC-1, natalizumab, IDEC-131, VLA-1; CAT-152; J695, CAT-192, CAT-213, BR3-Fc, LymphoStat-B, TRAIL-R1mAb, bevacizumab, ranibizumab, omalizumab, efalizumab, MLN-02, zanolimumab, HuMax-IL 15, HuMax-Inflam, HuMax-Cancer, HuMax-Lymphoma, HuMax-TAC, clenoliximab, lumiliximab, BEC2, IMC-1C11, DC101, labetuzumab, arcitumomab, epratuzumab, tacatuzumab, MyelomaCide, LkoCide, ProstaCide, ipilimumab, MDX-060, MDX-070, MDX-018, MDX-1106, MDX-1103, MDX-1333, MDX-214, MDX-1100, MDX-CD4, MDX-1388, MDX-066, MDX-1307, HGS-TR2J, FG-3019, BMS-66513, SGN-30, SGN-40, tocilizumab, CS-1008, IDM-1, golimumab, ONTO 1275, ONTO 95, ONTO 328, mepolizumab, MOR101, MOR102, MOR201, visilizumab, HuZAF, volocixmab, ING-1, MLN2201, daclizumab, HCD122, CDP860, PRO542, C14, oregovomab, edrecolomab, etaracizumab, siplizumab, lintuzumab, Hu1D10, Lym-1, efalizumab, ICM3, galiximab, eculizumab, pexelizumab, LDP-01, huA33, WX-G250, sibrotuzumab, Chimeric KW-2871, hu3S193, huLK26; bivatuzumab, ch14.18, 3F8, BC8, huHMFG1, MORAb-003, MORAb-004, MORAb-009, denosumab, PRO-140, 1D09C3, huMikbeta-1, NI-0401, NI-501, cantuzumab, HuN901, 8H9, chTNT-1/B, bavituximab, huJ591, HeFi-1, Pentacea, abagovomab, tositumomab, 105AD7, GMA161 and GMA321.

In other embodiments, the constant domain/first portion of the constructs can comprise a polypeptide having medicinal properties, such as agents that stimulate the immune system, in particular in relation to the ability of the immune system to attack tumor cells. These polypeptides can include cytokines (such as interleukin-2) or growth factors that stimulate immune cells directly or indirectly (i.e. act by providing gas to the immune system), as well as ectodomains or other binding agents that neutralize ligands which inhibit immune cells, either directly or indirectly (i.e. act by releasing a brake on the immune system).

In other embodiments, the constant domain/first portion of the constructs can comprise a polypeptide that does not have active medicinal properties pe se, but rather provides a localization signal. This localization motif will serve to focus the intrinsic TGF-β neutralization activity of the second portion of the construct to a particular region of the body. In one example, the first portion comprised a long poly-aspartate bone-localization motif, preferably D10 or an equivalent bone-localization moiety, which acts to enhance localisation of the construct to bone. By increasing the TGF-β neutralization activity of the construct within bone, more favourable dosing levels and schedules may be required for the treatment of bone-related diseases, such as osteogenesis imperfecta, relative to that required for a similar construct without the D10 motif.

Embodiments exemplifying polypeptide constructs of the present invention that include antigen-binding fragments at the N-terminus of the Fc region (first portion) are selected from the group consisting of SEQ ID NO: 121-131, and a sequence substantially identical thereto.

In other embodiments, polypeptide constructs of the present invention that include other targeting agents, e.g., a poly-aspartate bone-localization motif, at the N-terminus of the Fc region (first portion), are exemplified by SEQ ID NO: 136-150.

The polypeptide construct of the present invention may also comprise additional sequences to aid in expression, detection or purification of a recombinant antibody or fragment thereof. Any such sequences or tags known to those of skill in the art may be used. For example, and without wishing to be limiting, the antibody or fragment thereof may comprise a targeting or signal sequence (for example, but not limited to ompA), a detection/purification tag (for example, but not limited to c-Myc, His_5, His_6, or His_8G), or a combination thereof. In another example, the signal peptide may be MVLQTQVFISLLLWISGAYG (SEQ ID NO:89) or MDWTWRILFLVAAATGTHA (SEQ ID

NO:90). In a further example, the additional sequence may be a biotin recognition site such as that described in [WO/1995/04069] or in [WO/2004/076670]. As is also known to those of skill in the art, linker sequences may be used in conjunction with the additional sequences or tags, or may serve as a detection/purification tag.

The present invention also encompasses nucleic acid sequences encoding the molecules as described herein. Given the degeneracy of the genetic code, a number of nucleotide sequences would have the effect of encoding the desired polypeptide, as would be readily understood by a skilled artisan. The nucleic acid sequence may be codon-optimized for expression in various micro-organisms. The present invention also encompasses vectors comprising the nucleic acids as just described, wherein the vectors typically comprise a promoter and signal sequence that are operably linked to the construct-encoding polynucleotide for driving expression thereof in the selected cellular production host. The vectors can be the same or different provided both result in secretion of the dimeric polypeptide construct.

Furthermore, the invention encompasses cells, also referred to herein as transgenic cellular host, comprising the nucleic acid and/or vector as described, encoding a first polypeptide construct. The host cells may comprise a second nucleic acid and/or vector encoding a second polypeptide construct different from the first polypeptide construct. The co-expression of the first and second polypeptide constructs may lead to the formation of heterodimers.

The present invention also encompasses a composition comprising one or more than one polypeptide construct as described herein. The composition may comprise a single polypeptide construct as described above, or may be a mixture of polypeptide constructs. The composition may also comprise one or more than one polypeptide construct of the present invention linked to one or more than one cargo molecule. For example, and without wishing to be limiting in any manner, the composition may comprise one or more than one polypeptide construct of the present invention linked to a cytotoxic drug in order to generate an antibody-drug conjugate (ADC) in accordance with the present invention.

The composition may also comprise a pharmaceutically acceptable diluent, excipient, or carrier. The diluent, excipient, or carrier may be any suitable diluent, excipient, or carrier known in the art, and must be compatible with other ingredients in the composition, with the method of delivery of the composition, and is not deleterious to the recipient of the composition. The composition may be in any suitable form; for example, the composition may be provided in suspension form, powder form (for example, but limited to lyophilised or encapsulated), capsule or tablet form. For example, and without wishing to be limiting, when the composition is provided in suspension form, the carrier may comprise water, saline, a suitable buffer, or additives to improve solubility and/or stability; reconstitution to produce the suspension is effected in a buffer at a suitable pH to ensure the viability of the antibody or fragment thereof. Dry powders may also include additives to improve stability and/or carriers to increase bulk/volume; for example, and without wishing to be limiting, the dry powder composition may comprise sucrose or trehalose. In a specific, non-limiting example, the composition may be so formulated as to deliver the antibody or fragment thereof to the gastrointestinal tract of the subject. Thus, the composition may comprise encapsulation, time-release, or other suitable technologies for delivery of the antibody or fragment thereof. It would be within the competency of a person of skill in the art to prepare suitable compositions comprising the present compounds.

The constructs of the present invention may be used to treat diseases or disorders associated with over-expression or over-activation of ligands of the TGF-β superfamily. The disease or disorder can be selected from, but not limited to, cancer, ocular diseases, fibrotic diseases, or genetic disorders of connective tissue.

In the field of cancer therapy, it has recently been demonstrated that TGF-β is a key factor inhibiting the antitumor response elicited by immunotherapies, such as immune checkpoint inhibitors (ICI's) (Hahn & Akporiaye, 2006). Specifically, therapeutic response to ICI antibodies results primarily from the re-activation of tumor-localized T-cells. Resistance to ICI antibodies is attributed to the presence of immunosuppressive mechanisms that result in a dearth of T-cells in the tumor microenvironment. Thus, it is now recognized that in order to elicit responses in resistant patients, ICI antibodies need to be combined with agents that can activate T-cells and induce their recruitment into the tumor, i.e. reversing of the "non-T-cell-inflamed" tumor phenotype. One publication noted that overcoming the non-T-cell-inflamed tumor microenvironment is the most significant next hurdle in immuno-oncology (Gajewski, 2015).

We have shown using a proof-of-principle TGF-β trap, T22d35, that blocking of TGF-β effectively reverses the "non-T cell inflamed" tumor phenotype (Zwaagstra et al, 2012). This positions anti-TGF-β molecules as potential synergistic combinations with ICI's and other immunotherapeutics. In support of this, a 2014 study (Holtzhausen et al., ASCO poster presentation) examined effects of a TGF-β blocker when combined an anti-CTLA-4 antibody in a physiologically-relevant transgenic melanoma model. The study demonstrated that while anti-CTLA-4 antibody monotherapy failed to suppress melanoma progression, the combination of the TGF-β antagonist and anti-CTLA-4 antibody significantly and synergistically suppressed both primary melanoma tumor growth as well as melanoma metastasis. These observations correlated with significant increases in effector T-cells in melanoma tissues.

Fibrotic diseases include those that affect any organ of the body, including, but not limited to kidney, lung, liver, heart, skin and eye. These diseases include, but are not limited to, chronic obstructive pulmonary disease (COPD), glomerulonephritis, liver fibrosis, post-infarction cardiac fibrosis, restenosis, systemic sclerosis, ocular surgery-induced fibrosis, and scarring.

Genetic disorders of connective tissue include, but are not limited to, Marfan syndrome (MFS) and Osteogenesis imperfecta (OI).

The present invention will be further illustrated in the following examples. However, it is to be understood that these examples are for illustrative purposes only and should not be used to limit the scope of the present invention in any manner.

Example 1: Production and Purification of Fusion Molecules

Several fusion molecules comprising full-size antibody (FSA), V_HH-IgG Fc, D10-Fc or "headless" Fc C-terminally-fused to the T22d35 or T2m ectodomains were constructed (Table 1). All constructs comprising a heavy chain included the signal sequence MDWTWRILFLVAAATGTHA (SEQ ID NO:89) at the N-terminus, while constructs comprising a light chain included the signal sequence MVLQTQVFIS-

LLLWISGAYG (SEQ ID NO:90) at the N-terminus. The DNA coding for constructs were prepared synthetically (Biobasic Inc. or Genescript USA Inc.). Constructs comprising FSA, D10-Fc and "headless" Fc were cloned into the EcoR1 (5' end) and BamH1 (3' end) sites and those comprising V_HH-IgG Fc were cloned into the HindIII (5' end) and BamH1 (3' end) sites of the pTT5 mammalian expression plasmid vector (Durocher et al, 2002).

TABLE 1

FSA-, V_HH-IgG Fc-, D10-Fc- and Fc-fusion constructs produced. The letter in brackets in the construct column refers to the type of construct as illustrated in FIG. 2.

Construct	ED	Fusion Scaffold	Antibody source	Construct SEQ ID NO:
Cet-T2m (F)	T2m	FSA (hIgG1)	Cetuximab	121, 123
Cet-T22d35 (D)	T22d35	FSA (hIgG1)	Cetuximab	121, 122
Her-T22d35 (D)	T22d35	FSA (hIgG1)	Herceptin	124, 125
Ava-T22d35 (D)	T22d35	FSA (hIgG1)	Avastin	126, 127
Syn-T22d35 (D)	T22d35	FSA (hIgG1)	Synagis	128, 129
FC5-Fc-T22d35 (E)	T22d35	VHH-Fc (mIgG2)	FC5-Fc	130
FC5-Fc-T2m (G)	T2m	VHH-Fc (mIgG2)	FC5-Fc	131
D10-Fc-T2m (G) (several variants with differing D10 linkage and IgG isotype)	T2m	Fc	huIgG	136-139
Fc-T22d35 (A) (several variants with differing N-termini and IgG isotype)	T22d35	Fc	huIgG	100, 105
Fc-T2m (C) (several variants with differing N-termini and IgG isotype)	T2m	Fc	huIgG	91-97
T2m-Fc (R&D) (B)	T2m	Fc	huIgG1	132
T2m-Fc (B)	T2m	Fc	huIgG2	133

The Cet-T2m and Cet-T22d35 constructs were produced by transient co-transfection of Chinese Hamster Ovary (CHO) cells with the heavy chain (HC)-T2m or (HC)-T22d35 construct combined with the Cetuximab light chain (LC) construct which then assembled as the Cetuximab-T22d35 (Cet-T22d35) or Cetuximab-T2m (Cet-T2m) fusion molecules. Briefly, CetHC-T22d35 (SEQ ID NO:122) and CetLC (SEQ ID NO:121) plasmid DNAs (ratio=3:2) were co-transfected into a 10 L Wavebag culture of CHO-3E7 cells in FreeStyle F17 medium (Invitrogen) containing 4 mM glutamine and 0.1% Kolliphor p-188 (Sigma) in a Wavebag maintained at 37° C. Transfection conditions were: DNA (50% HC+LC plasmids, 30% ssDNA, 15% AKT plasmid, 5% GFP plasmid): PEI(polyethylenimine)pro (Polyplus) (ratio=1:2.5). At 24 hours post-transfection, 10% Tryptone N1feed (TekniScience Inc.) and 0.5 mM Vaporic acid (VPA, Sigma) were added and the temperature was shifted to 32° C. to promote the production and secretion of the fusion proteins and maintained for 15 days post transfection after which the cells were harvested. At final harvest the cell viability was 89.6%. The harvest supernatant (10.8 L) was filtered (0.2 μm) and loaded onto a 55 mL Protein A MabSelect Sure 55 mL column (GE Healthcare). The column was washed with 2 column volumes of PBS and protein was eluted with 3 column volumes of 0.1 M sodium citrate pH 3.6. To maximize the yield, the flow through was reloaded onto the Protein A column and eluted as described above. Eluted fractions were neutralized with 1 M Tris, evaluated by SDS-PAGE and those containing Cet-T22d35 were pooled (FIG. 3A) and subsequently loaded onto a Hi-load Superdex S200 26/60 size exclusion chromatography (SEC) column (GE Healthcare) equilibrated in formulation buffer (DPBS without Ca^{2+}, without Mg^{2+}). Protein was eluted using 1 column volume formulation buffer, collected into successive fractions and detected by UV absorbance at 280 nM (FIG. 3B). The main peak SEC fractions containing Cet-T22d35 protein were then pooled and concentrated to a concentration of 7.8 mg/mL. The final yield was 533 mg.

Similar transfection, production and purification methods were performed for the other FSA-trap examples listed in Table 1. In the case of the V_HH-Fc IgG-, D10 and "headless" Fc-fusion molecules the composition of the transfection mixture was modified as follows: DNA (80% plasmid construct, 15% AKT plasmid, 5% GFP plasmid): PEIpro (ratio 1:2.5).

The integrity of the pooled Prot-A and SEC fractions of Cet-T22d35 protein was analyzed by SDS-PAGE (4-15% polyacrylamide) under reducing and non-reducing conditions (FIG. 3C) and by UPLC-SEC (FIG. 3D). For UPLC-SEC, 2-10 μg of protein in DPBS (Hyclone, minus Ca2+, minus Mg2+) was injected onto a Waters BEH200 SEC column (1.7 μm, 4.6×150 mm, SN:01773430816818) and resolved under a flow rate of 0.4 mL/min for 8.5 min at room

temperature, using the Waters Acquity UPLC H-Class Bio-System. Protein peaks were detected at 280 nM (Acquity PDA detector). Coomassie brilliant blue (CBB) staining of the gels shows the CetHC-T22d35 (~110 Kd) and CetLC bands (~30 Kd) under reducing conditions while under non-reducing conditions a 250 Kd band is detected which represents the fully assembled and highly pure Cet-T22d35 fusion protein. Additional UPLC-SEC analysis of the SEC purified, pooled ProtA sample confirmed the high degree of purity (99.42%) of the Cet-T22d35 protein and the absence of aggregates. Together, these results demonstrate the manufacturability of the Cet-T22d35 fusion protein.

Similar methods were used to analyse expression levels, purifiability, aggregation levels, and dimeric assembly of several other Fc-ectodomain constructs. The results from these studies are shown in FIG. **3** E to L.

FIG. **3**E to **3**H show the results from the analysis of the hIgG1FcΔK(C)-T2m construct (an example of Type C construct from FIG. **2**). FIG. **3**E shows the (ProtA)-affinity column elution profile. Fraction 12-15 were pooled, subjected to a UPLC-SEC evaluation (FIG. **3**F), further SEC purified to remove aggregates and re-evaluated by UPLC-SEC (FIG. **3**G). This confirmed the high degree of purity of the hIgG1FcΔK(C)-T2m construct and the absence of aggregates. SDS-PAGE (FIG. **3**H) under non-reducing (NR) and reducing (R) conditions shows bands of expected molecular weights, demonstrating the expected assembly of hIgG1FcΔK(C)-T2m as a disulphide linked dimer.

FIGS. **3**I and **3**J compare the level of aggregation of two "headless" Fc-T2m constructs (examples of Type C in FIG. **2**). The Fc-T2m construct is an IgG2-based construct without engineering of the hinge region, thus it contains four cysteine residues, whereas the hIgG2FcΔK(CC)-T2m has been engineered by N-terminal truncation of the hinge region to have only two cysteines in the hinge region. It can be seen that the Fc-T2m construct contains a high level of aggregates after Protein A purification, with a doublet peak remaining even after further SEC purification. In contrast, hIgG2FcΔK(CC)-T2m, which has an engineered N-terminus, exhibited low levels of aggregates after only Protein A purification. These results demonstrate the advantage of carrying out N-terminal engineering of headless Fc-T2m constructs to reduce aggregation.

FIGS. **3**K and **3**L compare the level of aggregation of two "headless" Fc-T22d35 constructs (examples of Type A in FIG. **2**). The Fc-T22d35 construct is without engineering of the hinge-region cysteine residues whereas the hIgG1 FcΔK (C)-T22d35 construct has been engineered by N-terminal truncation of the hinge to have only one cysteine in the hinge region. It can be seen that, similarly to Fc-T2m, the Fc-T22d35 construct contains a high level of aggregates after Protein A purification, with a doublet peak remaining as detected by UPLC-SEC even after further SEC purification. In contrast, hIgG1FcΔK(C)-T22d35, which has an engineered N-terminus, exhibited lower levels of aggregates after Protein A purification. Further SEC purification yielded a singlet peak as detected by UPLC-SEC, confirming the absence of aggregates. These results demonstrate the advantage of carrying out N-terminal engineering of headless Fc-T22d35 constructs to reduce aggregation.

Example 2: Neutralization and Binding of TGF-β by Fusion Constructs

The TGF-β neutralization potencies of purified Fc-ectodomain fusion constructs were determined and compared to those of non-Fc-fused T22d35. It should be noted that non-Fc-fused T2m does not neutralize any of TGF-β1, -β2, or -β3 (De Crescenzo et al, 2001).

TGF-β neutralization potencies for TGF-β1, -β2 and -β3 were determined for purified fusion constructs using two cell-based signaling assays: 1) the Mv1 Lu cell luciferase reporter assay with Mv1 Lu cells having a PAI-1-luciferase reporter (as described in (Zwaagstra et al, 2012)) and an A549 cell/IL-11 release assay adapted to the MSD (Meso Scale Discovery) platform.

Mv1Lu cell luciferase reporter assay: Briefly, cells were seeded onto 96-well plates (20,000 cells/well) and then treated with T2m, T22d35, or a fusion construct+25 pM TGF-β at 37° C. for 16 h in DM EM, 1% FBS, 0.1% BSA. Cells were then lysed and luciferase activity was measured (Promega Corp.) using a Synergy 2 plate reader (BioTek Instruments Inc.).

A549 cell IL-11 release assay: Human A549 lung cancer cells (ATCC-CCL-185, Cedarlane Burlington ON) were seeded in 96-well plates (5×103 cells/well). The following day 10 pM TGF-β in complete media in the absence or presence of a serial dilution of fusion protein was incubated for 30 min at RT prior to adding to the cells. After 21 h of incubation (37° C., 5% CO2, humidified atmosphere) conditioned medium was harvested and added to MSD Streptavidin Gold plates (Meso Scale Diagnostics, Gaithersburg, MD) that were coated with 2 μg/mL biotinylated mouse anti-human IL-11 antibody (MAB618, R&D Systems, Minneapolis, MN). After 18 h (4° C.) plates were washed with PBS containing 0.02% Tween 20, a 2 μg/mL SULFO-tagged goat anti-human IL-11 antibody (AF-218-NA, R&D Systems Minneapolis, MN) was added and plates were incubated for 1 h at RT. After a final wash, plates were read in a MESO QuickPlex SQ120 machine (Meso Scale Diagnostics, Gaithersburg, MD). IL-11 readouts were expressed as percent IL-11 release compared to control cells treated with TGF-β alone.

In one set of experiments, using the Mv1Lu cell reporter assay, the neutralization potency of Cet-T2m (construct Type F in FIG. **2**), Cet-T22d35 (construct Type D in FIG. **2**) and T**22**d35 (non-Fc-fused) were compared. FIG. **4**A shows representative TGF-β1 (top panel), TGF-β3 (middle panel) and TGF-β2 (bottom panel) neutralization curves for Cet-T2m, Cet-T22d35 and T22d35 while Table 2 summarizes TGF-β1, -β2 and -β3 neutralization IC_{50} values. Unexpectedly, the TGF-β1 and TGF-β3 neutralization curves for the Cetuximab fusion constructs indicated extremely high potencies that lie in the picomolar range (determining a single IC_{50} value in these experiments is difficult due to the biphasic nature of the curves). The observed TGF-β1 IC_{50} value for Cet-T22d35 was in the picomolar range. In contrast, the TGF-β1 IC_{50} for non-Fc-fused T22d35 was approximately 1 nM. This illustrates that there is a large increase in T22d35 potency upon fusion to the C-terminus of the Fc region of Cetuximab (due to the biphasic nature of the Cet-T22d35 curve, the fold difference is difficult to determine in these experiments). The TGF-β1 IC50 value for Cet-T2m was also subpicomolar (but less potent than Cet-T22d35), whereas unfused T2m is not able to detectably neutralize TGF-β1, even at concentrations above 500 nM (De Crescenzo et al, 2001). This demonstrates that, similar to T22d35, a very significant increase in T2m potency occurs upon fusion to the C-terminus of the Fc region of Cetuximab. Both Cet-T22d35 and Cet-T2m neutralized TGF-β2 (IC_{50}~nM range), whereas T22d35 and T2m (De Crescenzo et al, 2001) alone did not, even at a concentration of 800 nM,

again showing the remarkable increase in neutralization potency that occurs upon fusion of T22d35 or T2m to the C-terminus of an Fc region.

In another set of experiments using the Mv1 Lu cell reporter assay, similar extremely high potencies of TGF-β neutralization were observed for other C-terminus Fc fusion constructs (Table 2), e.g. for constructs in which T22d35 or T2m were fused with FSAs such as Herceptin (Her-T22d35), Avastin (Ava-T22d35) or Synagis (Syn-T22d35) [Type F and D constructs in FIG. **2**], or with the blood-brain barrier crossing Fc-fused FC5 V_HH antibody (FCS-Fc-T22d35 and FC5-Fc-T2m) [Type E and G constructs in FIG. **2**]. In addition, fusion of T22d35 or T2m to the C-terminus of an IgG2-Fc region alone, i.e. an antibody with no Fab region present (Fc-T22d35 and Fc-T2m) [Type A and C constructs in FIG. **2**] resulted in fusion proteins with similarly high neutralization potencies. However, fusing T2m to the N-terminus of an IgG2-Fc (T2m-Fc) generates a fusion protein that does not neutralize TGF-β1 and -β3 in the picomolar range, but rather in the range of 1 nanomolar (0.3 to 15 nM in Table 2) and lacks any activity towards TGF-β2. These results are similar to those obtained with commercially available N-terminally IgG1 Fc-fused TGF-β Type II receptor ectodomain (T2m-Fc (R&D Systems)) (0.3 to 0.5 nM in Table 2). Together, these results thus demonstrate that fusion of TGF-β superfamily receptor ectodomains to the C-terminus of an Fc domain in the context of full-size antibodies, a V_HH-Fc, or an Fc region alone, give rise to unexpectedly high TGF-β neutralization potencies.

TABLE 2

TGF-β neutralization IC_{50} of fusion constructs. It should be noted that T2m does not neutralize any of TGF-β1, -β2, or -β3 (De Crescenzo et al, 2001). It should also be noted that the IC_{50} values in the table below are estimates due to the biphasic nature of the curves.

	TGF-β1 Av IC_{50} (nM)	TGF-β3 Av IC_{50} (nM)	TGF-β2 Av IC_{50} (nM)
Cet-T22d35	0.000, 001	0.000, 002	13.6
Cet-T2m	0.000, 1	0.000, 0015	129.2
T22d35	1.232	0.033	No neutralization
Her-T22d35	0.000, 13	0.000, 05	7.89
Ava-T22d35	0.000, 000, 72	0.000, 00038	8.60
Syn-T22d35	0.000, 042	0.000, 0001	35.2
FC5-Fc-T22d35	0.000, 001	0.000, 001	96.2
FC5-Fc-T2m	0.000, 017	0.000, 015	432.9
Fc-T22d35	0.001, 445	0.000, 026	108.4
T2m-Fc (R&D)	0.506	0.323	No neutralization
T2m-Fc	14.523	0.276	No neutralization
Fc-T2m	0.009, 923	0.000, 766	460.5

In order to confirm the relative potencies of Fc-ectodomain constructs, a second cell-based assay, an A549 cell IL-11 release assay, was used. This IL-11 release assay acts as a model of TGF-β-mediated biological responses that contribute to both tumor metastasis and fibrosis. In the set of experiments shown in FIG. **4**B, the neutralization potencies of T22d35, Fc-T2m, Fc-T22d35, Cet-T22d35, Her-T22d35, Ava-T22d35, Syn-T22d35 and FCS-Fc-T22d35 were compared. It can be seen that the neutralization curves in this assay are not biphasic, making it less challenging than the Mv1Lu assay to determine and compare IC_{50} values. All of the constructs in which T22d35 was fused to the C-terminus of an Fc region exhibited IC_{50} values in the range of 5 pM, corroborating the extremely high potency observed for these constructs in the Mv1Lu assay. It can also be seen in FIG. **4**B that the IC_{50} value for non-Fc-fused T22d35 was ~0.5 nM. This indicates that a ~100-fold increase in potency occurs upon fusion of T22d35 to the C-terminus of an Fc region. The IC_{50} value for Fc-T2m was 0.05 nM. This indicates that constructs with two ectodomains in the C-terminal portion may be more potent than a construct with one ectodomain in the C-terminal portion (as was observed in the Mv1Lu assay, FIG. **4**A), however, it should be noted that Fc-T2m does not have an optimized N-terminus.

An additional set of experiments in which the A549 cell IL-11 release assay was used to compare TGF-β neutralization potencies is shown in FIG. **4**C. Here, the potencies of several "headless"-T2m constructs were assessed along with that of non-Fc-fused T22d35. The potency of T22d35 was determined to be ~0.5 nM, consistent with the data shown in FIG. **4**B. This is illustrative of the robustness of the A549 cell IL-11 release assay. It can also be seen in FIG. **4**C that all of the "headless"-T2m constructs exhibited high potencies with IC_{50}s in the range of 5 pM (3 to 17 pM). These values are in the same range as those of the T22d35-containing constructs shown in FIG. **4**B, and are 10-fold higher potency than that of the "headless"-T2m containing construct also shown in FIG. **4**B (Fc-T2m). Since all of the T2m-containing constructs in FIG. **4**C have engineered N-termini, whereas Fc-T2m does not, these results indicate that engineering of the cysteine residues of the hinge region of "headless" constructs is able to increase their potency by approximately 10-fold.

We have also compared the potencies of constructs that include three TβRII structured ectodomains with constructs carrying two ectodomains using the A549 cell IL-11 release assay. We observed that the triple-repeat based constructs (SEQ ID NO:111 and SEQ ID NO:116) are potent in neutralizing TGF-β1 in this assay, and typically have improved IC50 values relative to the corresponding double-repeat based constructs (SEQ ID NO:100 and

SEQ ID NO:106, respectively). All constructs involved in this comparative study had the same engineered N-terminus of the Fc portion, hIgG1FcΔK(C).

Binding to TGF-β: Binding of T22d35, Cet-T22d35, and Cet-T2m to TGF-β2 was measured using a competitive SPR binding experiment. In this assay, the molecule of interest was first allowed to bind to a fixed amount of TGF-β in solution. A 2-fold dilution series was prepared in PBS-0.05% Tween, starting with 1000 nM T22d35 trap or 20 nM Cet-T22d35 or Cet-T2m. Each diluted sample was pre-incubated with 1 nM TGF-β2 for 30 min at room temperature to allow binding. The mixture was then flowed over immobilized, pan-specific anti-TGF-β antibody 1D11 (2000 RU 1D11) in order to quantify the amount of ligand left unbound (TβRII ectodomain and 1D11 bind to a similar epitope on TGF-β) using a Biacore T200 instrument. The TGF-β2 binding EC_{50} values were determined by plotting the percent free TGF-β versus the protein concentration of the molecule of interest. Binding curves and EC_{50} values are shown in FIG. **4**D and Table 3. In the case of TGF-β2 binding, a 100-fold increase in binding was observed between Cet-T22d35 and unfused T22d35 (EC_{50}~1 nM versus>100 nM, respectively), indicating that C-terminal fusion of the T22d35 trap to antibody provides a gain in affinity for the TGF-β2 isoform. This correlates with the ability of Cet-T22d35 to neutralize TGF-β2 in the 10 nM range, and the inability of unfused T22d35 to neutralize TGF-β2, as observed in the Mv1 Lu-Luc cell reporter assay.

TABLE 3

EC_{50} of Cetuximab-trap binding to TGF-β in solution. EC_{50} is the Effective Concentration at which 50% of TGF-β is bound and is given in nM. Note: T2m alone shows an IC50 of greater than 1000 nM (Zwaagstra et al, 2012), and thus is not considered neutralizing.

Trap variant	EC_{50} for TGF-β2
T22d35	>100
Cetuximab-T2m	1.17
Cetuximab-T22d35	0.50

Example 3A: Validation of Antibody Binding

The ability of an antibody alone or in a fusion construct of Example 1 to bind to its intended target antigen was evaluated using surface plasmon resonance (SPR).

Direct binding of Cet-T22d35 or Cetuximab to the EGF receptor extracellular domain (EGFR-ED) was quantified by SPR using a BIAcore T200 instrument, performed in the standard manner. Briefly, Cet-T22d35 or Cetuximab alone were captured on the SPR CM5 chip using immobilized anti-human IgG Fc-specific antibody (2000 RU). Variable concentrations of EGFR-ED in PBS-0.05% Tween were then flowed over the capture surface at 100 μl/min and 25° C. The resulting sensorgrams (data not shown) were analyzed using the Biacore T200 evaluation software. The K_D values of Cet-T22d35 and Cetuximab were very similar (847 and 708 pM, respectively), indicating that fusion of T22d35 to the Fc portion of Cetuximab does not appreciably alter binding to EGFR-ED, compared to the non-fused FSA. Similar SPR methods and analyses were performed for other antibody-trap fusion examples, compared with their corresponding target antigens (see Table 4).

From Table 4 it is evident for each exemplified construct that fusion of a TGF-β superfamily receptor ectodomain(s) to the C-terminus of the Fc region of an antibody did not significantly alter antigen-binding affinities and K_D values of the antibody. This indicates that the ectodomain(s) can be readily fused to any antibody without compromising the ability the antibody to bind its target antigen.

TABLE 4

SPR determination of antigen-binding affinity of T22d35 fusion constructs or antibodies alone. NOTE: FC-5-Fc, FC5-Fc-T2m, and FC-5-Fc-T22d35 binding affinity was assessed via the transwell functional assay (see Example 3C).

	Antigen	K_a (1/Ms)	K_d (1/s)	K_D (M)
Cetuximab-T22d35	EGFR	1.22×10^6	8.65×10^{-4}	7.08×10^{-10}
Cetuximab	EGFR	1.03×10^6	8.45×10^{-4}	8.47×10^{-10}
Her-T22d35	Her2	8.30×10^4	5.30×10^{-5}	6.37×10^{-10}
Herceptin	Her2	6.88×10^4	5.03×10^{-5}	7.33×10^{-10}
Syn-T22d35	RSV-F	3.55×10^4	1.42×10^{-3}	4.10×10^{-9}
Synagis	RSV-F	2.57×10^4	1.68×10^{-3}	6.60×10^{-9}

Example 3B: Validation of Cetuximab Function

The ability of Cetuximab to maintain its therapeutic function (i.e. inhibition of EGF-induced EGFR phosphorylation and signaling) when fused to either T2m or T22d35 (Example 1) was evaluated.

Phosphorylation of EGFR: The ability of Cetuximab-comprising constructs to inhibit EGF-induced phosphorylation of EGFR in human lung cancer A549 cells was evaluated. A549 cells were seeded in 24-well plates (100,000 cells/well) and either mock treated (−) or pre-treated with Cetuximab, Cet-T2m, or Cet-T22d35 (all at 10, 1 or 0.1 nM) or T22d35 (10 nM) at 37° C. for 3 h, then treated with 50 ng/mL EGF at 37° C. for 10 min. Whole cell lysates were prepared and resolved by SDS-PAGE, western blotted and probed with anti-phosphoTyrosine antibody (Clone 4G10, Millipore 05-321). As shown in FIG. **5**A, Cetuximab and Cet-T2m and Cet-T22d35 inhibited EGFR phosphorylation to similar extents, whereas T22d35 had no effect, relative to the +EGF control. These results thus confirm that the TGF-β superfamily receptor ectodomain moieties in Cetuximab-T2m and Cetuximab-T22d35 fusion proteins do not interfere with the function of the Cetuximab antibody (i.e. inhibition of EGF induced EGFR signaling).

Inhibition of EGFR signaling: Inhibition of autocrine EGFR signaling results in varying degrees of cytotoxicity in EGFR-expressing cells treated with Cetuximab. Cytotoxicity of Cet-T22d35 was compared to Cetuximab and T22d35 in human breast cancer cells (MDA-MB-468) and immortalized keratinocyte cells (HaCaT). These cells exhibited significant Cetuximab cytotoxicity, due to their intrinsic dependence on the EGF signaling pathway for basal growth.

The cells were seeded onto 96-well plates (MDA-MB-468, 2300 cells/well; HaCaT, 1500 cells/well) and then treated with different doses of inhibitor at 37° C. for 5 days. Cell viability was measured using sulforhodamine reagent to determine the percentage of viable cells relative to mock-treated controls. Results are shown in FIG. **5**B and Table 5. The IC_{50} values for Cet-T22d35 and Cetuximab were similar in both cell lines (0.2-1.4 nM range), while T22d35 resulted in no cytotoxicity. These results further confirm that the TGF-β superfamily receptor ectodomain moiety in Cetuximab-T22d35 does not interfere with the function of the Cetuximab antibody.

TABLE 5

Cetuximab-T22d35 cytotoxicity in MDA-MB-468 and HaCat cells. The cytotoxic potency IC_{50} values are given in nM.

	MDA-MB-468 IC_{50}	HaCaT IC_{50}
Cetuximab	0.50	0.33
Cetuximab-T22d35	1.42	0.22
T22d35	0	0

Example 3C: Validation of FC5 Function

The ability of FC5 V_HH to maintain its function (i.e. transmigrate the blood-brain barrier) when fused with the T2m or T22d35 moieties (see description in Example 2 and activities in Table 2) was evaluated.

Briefly, SV40-immortalized Adult Rat Brain Endothelial Cells (Sv-ARBEC) were used to generate an in vitro blood-brain barrier (BBB) model as described (Garberg et al, 2005; Haqqani et al, 2013). Sv-ARBEC cells (80,000 cells/membrane) were seeded on 0.1 mg/mL rat tail collagen type I-coated tissue culture inserts (pore size-1 μm; surface area 0.9 cm^2, Falcon) in 1 ml of growth medium. The bottom chamber of the insert assembly contained 2 ml of growth medium supplemented with the immortalized neonatal rat astrocytes-conditioned medium in a 1:1 (v/v) ratio. Equimolar amounts (5.6 μM) of positive (FC5-Fc) control; negative controls (A20.1); and T22d35, T2m, FC5-Fc-T22d35 or FC5-Fc-T2m were tested for their ability to cross

the Sv-ARBEC cell monolayer. Following exposure of equimolar amounts of the proteins to the luminal side of the BBB, samples were taken after 15, 30, and 60 min from the abluminal side. The protein content of each sample was then quantified by mass spectrometry (multiple reaction monitoring-isotype labeled internal standards; MRM-ILIS) as described by (Haqqani et al, 2013) (see method description below).

Quantified values can be directly plotted or the P_{app} (apparent permeability coefficient) values can be determined using the following formula

$$Papp = \frac{dQr/dt}{A \times C_0}$$

The P_{app} value is commonly used to determine the specific permeability of a molecule, and is a measure of transport across the brain endothelial monolayer. [Qr/dt=cumulative amount in the receiver (bottom) compartment versus time; A=area of the cell monolayer; C0=initial concentration of the dosing solution (top chamber)].

FIG. **6** shows the results of the experiment. The P_{app} value of FC5-Fc-T22d35 was similar to the control FC5-Fc, indicating it was transported efficiently and that the fused T22d35 did not interfere with transport. The P_{app} value for FC5-Fc-T2m was approximately 50% less, compared to FC5-Fc-T22d35 and FC5-Fc, indicating somewhat reduced permeability. Nevertheless, the level of transport of FC5-Fc-T2m was about 4-fold greater than the negative controls (T2m, T22d35, and antibody A20.1).

Example 4: Inhibition of Epithelial to Mesenchymal Transition

Treatment of A549 cells with EGF plus TGF-β results in a strong epithelial to mesenchymal transition (EMT). The EMT is phenotypically characterized by changes in cell morphology (tight cellular junctions with "cobble-stone" appearance converts to elongated cells, see FIG. **7**A) and changes in the adherin junction proteins E-cadherin and N-cadherin. The ability of the fusion constructs to block EMT was assessed in A549 cells by western blotting (E-cadherin) and flow cytometry (E-cadherin and N-cadherin).

Briefly, for the western blot analysis, A549 cells were seeded in 24-well plates (8000 cells/well) and then treated with EGF (50 ng/mL)+TGF-β1 (50 pM) at 37° C. for 3 days in the presence of Cet-T22d35, Cetuximab, or T22d35 (0, 0.05, 0.5, 5, 50, or 500 nM). Whole cell lysates were prepared and resolved by SDS-PAGE. The proteins were transferred to nitrocellulose and then probed with an E-cadherin antibody (BD Transduction laboratories Biosciences) (FIG. **7**B). The E-Cadherin positive bands in the Western blot were quantified by densitometer detection and ImageJ analysis (FIG. **7**C). EGF+TGF-β treatment resulted in an EMT, as indicated by the disappearance of E-cadherin (compare non-treated and EGF+TGF-β lanes in the absence of inhibitors). Cet-T22d35 blocked the EMT (E-cadherin disappearance) in a dose-dependent manner whereas 500 nM Cetuximab or T22d35 treatments only modestly blocked the EMT (E-cadherin levels ~20-25% of the non-treated control level).

The ability of Cet-T22d35, Cetuximab and T22d35 to block the EGF+TGF-β EMT response was further examined by flow cytometry using A549 cells treated with Cet-T22d35 or Cetuximab, (all at 50, 5, 0.5 nM) or the Cetuximab+T22d35 combination (50 nM+100 nM, 5 nM+10 nM, or 0.5 nM+1 nM, respectively) and evaluating the EMT associated changes in E-cadherin and N-cadherin cell surface expression levels (FIG. **7**D). In this experiment the molar amounts of the molecules of interest used in 'T22d35 alone' and 'Cetuximab+T22d35' groups were two-fold higher than for Cet-T22d35 in order to correspond with a 2:1 trap/antibody ratio in the Cet-T22d35 fusion molecule. A549 cells were seeded in 6-well plates (30,000 cells/well) and pre-treated with the inhibitors at 37° C. for 1 h, followed by added treatment with EGF (10 ng/mL)+TGF-β (10 pM) and incubation at 37° C. for 3 days. Cells were then dissociated from the plate using 1 mL Dissociation Buffer (Sigma)/well, centrifuged at 2000 rpm for 2 min and re-suspended in 100 μl RPMI-5 media at 4° C. AlexaFluor488-E-cadherin (Santa Cruz, SC21791) and AlexaFluor647-N-cadherin (BD Biosciences, 563434) antibodies (1/25 v/v dilutions) were added and samples were incubated at 4° C. for 1 h. Cells were then centrifuged, washed once in RPMI-5, and re-suspended in 400 μl RPMI-5 containing 15 μg/mL propidium iodide (Life Technologies) at 4° C. Mean fluorescent intensities (MFI) were measured by flow cytometry (BD LS RII flow cytometer, BD Biosciences) to quantify E-cadherin and N-cadherin levels. The results show that Cet-T22d35 was more effective in preventing down-regulation of E-cadherin (FIG. **7**D, top panel) and up-regulation of N-cadherin (FIG. **7**D, bottom panel), as a measure of blocking EMT, compared to Cetuximab, T22d34 or the Cetuximab+T22d35 combination at each respective dose, and is most notable at the lowest dose used (0.5 nM).

Example 5: Pharmacokinetic (PK) Studies on Constructs with and without a Lysine Residue at the Fusion Site Between the C-Terminus of the Fc Region and the N-Terminus of the Ectodomain

PK studies were carried out in normal, healthy mice to determine whether fusion of T22d35 to an antibody increased its half-life in vivo, and whether removal of a lysine at the fusion site within constructs reduced the amount of cleavage occurring in vivo.

Results from Cet-T22d35 (construct Type D in FIG. **2**—containing a lysine at the fusion site): A single bolus of Cet-T22d35 protein (10 mgs/Kg) formulated in DPBS was intravenously injected (IV) into the tail vein of normal Balb/c mice and serum samples were collected from the submandibular vein at selected time points (0.5, 1, 2, 4, 8, 14, 24, 48, 96 h). Blood samples were centrifuged at 2000 g at 4° C. for 10 min and the serum supernatant was removed and stored frozen at −80° C., prior to analyses. The samples were thawed at 4° C. and analyzed via mass spectrometry (multiple reaction monitoring-isotype labeled internal standards; MRM-LIS) in order to measure the levels of both the Cetuximab and T22d35 trap moieties. Briefly, 20 μl of sample was thawed and treated with mild detergents (0.1% RapiGest SF, Waters; 5.5 mM TCEP) at 95° C. for 10 min. The sample was cooled to room temperature and Iodoacetamide (IAA) in 50 mM Ammonium Bicarbonate was added to a final concentration of 10 mM IAA, followed by incubation for 40 min in the dark. DTT (10 mM final) was then added and the sample was incubated at room temperature for 15 min, followed by trypsin digestion (Sigma, 0.8 mg/mL final) at 37° C. for 18 h. A mixture of 5 μM each of isotope-labeled trap and cetuximab peptides (formulated in 30% acetonitrile, 0.1% formic acid) were added to final concentrations of 1 μM, as internal standards for quantification. The isotope-labeled peptides were 13C/15N-(H2N-

LPYHDFILEDAASPK-OH; SEQ ID NO:134) and 13C/15N-(H2N-ALPAPIEK-OH; SEQ ID NO:135) for T22d35 and Cetuximab, respectively (NewEngland Peptide). Trifluoroacetic acid was then added (0.5% final), followed by incubation at 37° C. for 30 min. The samples were centrifuged at 13000 rpm for 20 min and the supernatant was used analyzed via MRM-ILIS using an Agilent 1260 HPLC system coupled with Agilent QQQ6410B at 55° C. The PK profiles seen in FIG. **8**A show that the levels of the Cetuximab and T22d35 moieties diverge at early time points (<10 h) after injection, indicating different kinetics and suggesting possible cleavage of T22d35 from the Cet-T22d35 protein in vivo. Nevertheless, analysis of these curves using a two compartmental model (Phoenix WinNonlin Software-Version 6.3) indicated that the average terminal half-life (T½β) of the T22d35 component was 45.8 h. This represents a 7.6-fold increase compared to the previously determined half-life for unfused T22d35 (T½β~6 h). As well, the PK profile shows that the Cetuximab moiety was maintained in the blood, with a T½β=262.5 h, indicating that the Cetuximab moiety has a long circulating half-life.

Results from several constructs with lysine deleted at the fusion site:

The same methods that were used in the PK study of Cet-T22d35 (FIG. **8**A) were applied to assess the PK of CetΔK-T2m (Type F in FIG. **2**) as well as several "headless" T2m constructs (Type C in FIG. **2**; hIgG1FcΔK(SS)-T2m, hIgG1FcΔK(ΔC)-T2m, and hIgG2FcΔK(SS)-T2m), all of which have the lysine deleted at the fusion site. The data shown in FIG. **8**B indicate that no detectable cleavage of these constructs is occurring in vivo since the levels of the Fc moieties (closed symbols) and ectodomain moieties (open symbols) do not diverge over time. Additionally, all of the constructs exhibit similar long circulating half-lives with T½ βs of approximately 100 h. This represents an improvement to the half-life of the ectodomain moiety of the construct which has a lysine at the fusion site, presented in FIG. **8**A (45.8 h).

Example 6: Efficacy Studies Comparing the Effect of "Headless" Fc-T2m and FSA-T2M Constructs on Tumor Growth (A) and T-Cell Function (B and C) in an Immune-Competent Syngeneic Triple Negative Breast Cancer (4T1) Model

A FSA-T2m construct (Cet-T2m—Type F in FIG. **2**) and three headless constructs, all with engineered N-termini, (hIgG1FcΔK(CC)-T2m, hIgG1 FcΔK(C)-T2m, and hIgG2FcΔK(CC)-T2m—Type C in FIG. **2**) were evaluated for their ability to inhibit tumor growth and to affect T-cell function in a syngeneic tumor model derived from 4T1 triple negative breast cancer cells. The results presented in FIG. **9** show the effect on tumor growth (A) and T-cell function (B, C). The effects of these Fc-fused ectodomain constructs were compared to those of a pan-specific neutralizing anti-TGF-β antibody, 1 D11 and a non-Fc-fused ectodomain construct, T22d35.

The protocols used for these syngeneic mouse model studies are described in (Zheng et al, 2013). Briefly, female BALB/c (H-2Kd) mice 6 weeks of age were purchased from The Jackson Laboratories and kept in filter-top cages. The 4T1 breast cancer cells and B16F10 cells were purchased from American type culture collection and cultured in RPMI-1640 supplemented with 2 mmol/L L-glutamine, 100 U/mL penicillin, 100 microgm/L streptomycin, 50 micromol/L 2-mercaptoethanol, and 10% fetal calf serum. Mice were inoculated subcutaneously in the left flank with 100 uL sterile saline containing 5×10^4 4T1 cells. Tumors were grown to ~100 mm^3, as measured by caliper, then mice were randomized and divided into the six treatment groups (8 animals/group) (Day 0). Treatments commenced on Day 1 and continued for 15 days with the animals being dosed at 5 mg/kg twice per week such that they received a total of 4 doses. Tumor growth was monitored by caliper measurements 3× per week. Animals were euthanized by exsanguination under anaesthesia on Day 15; T cells were isolated from draining lymph nodes and assessed for their capacity to kill mouse 4T1 and B16F10 tumour cells ex vivo. The capacity of T cells from mice treated with or without test agents to lyse target 4T1 tumor cells was measured using a CytoTox 96 nonradioactive cytotoxicity assay kit (Promega) according to the manufacturer's instructions. Briefly, naïve target 4T1 cells or melanoma cell line B16F10 cells are plated and incubated for 4 hr with CD8+ effector T cells isolated from 4T1 tumor-bearing mice using CD8 magnetic MicroBeads (BD Bioscience). The isolated CD8+ cells are confirmed, by flow cytometry, to be over 85% CD8+. A range of ratios of effectors to target cells is tested (100:1, 50:1, 25:1). Lactate dehydrogenase (LDH) release in response to effector T cells is measured in the buffer bathing target cells. Target cells incubated in the absence of effector cells are used as a comparator to control for spontaneous LDH release. Released LDH in culture supernatants is detected after a 30-min incubation using a coupled enzymatic assay. The intensity of the color formed is proportional to the number of lysed cells. Cytotoxic activity of CTL is calculated using the following formula:

Cytotoxic activity %=[(absorbance)−(spontaneous effector cell LDH release)−(spontaneous target cell LDH release)]/[(maximal LDH release)−(spontaneous target cell LDH release)]×100

The results presented in FIG. **9**A show the effect of the Fc-fused ectodomain constructs listed above on 4T1 tumor growth (the pan-specific neutralizing anti-TGF-β antibody, 1D11, and a non-Fc-fused ectodomain construct, T22d35, being tested as comparators). As can be seen in FIG. **9**A, all of the Fc-fused ectodomain constructs reduced tumor growth relative to the saline treatment when tested for significance by t-test. The 1D11 and T22d35 comparator treatments were observed to be less effective relative to the Fc-fused ectodomain treatments, and not significantly different from the saline control. These results demonstrate that constructs with an ectodomain fused to the C-terminus of an Fc region have significant anti-tumor potency, with the efficacy being higher than the 1D11 and T22d35 comparators. There was no significant difference between the FSA-T2m construct (Cet-T2m) and the constructs that have no Fab, i.e. are "headless" (hIgG1 FcΔK(CC)-T2m, hIgG1 FcΔK(C)-T2m, and hIgG2FcΔK(CC)-T2m) with respect to their effect on tumor growth. The high anti-tumor potency of these Fc-ectodomain fusions relative to comparators likely results from high potency neutralization of TGF-β combined with a favourable circulating half-life.

To investigate whether these Fc-ectodomain fusions exhibit an immuno-modulatory effect in vivo on cytotoxic T lymphocyte cells (CTLs) present in tumor draining lymph nodes, lymph nodes were removed from mice treated with or without test agents; T-cells were then isolated and tested for their capacity to lyse target 4T1 tumor cells (and B16F10 cells as a test of tumor specificity) using the methods described above.

As shown in FIG. **9**B, treatment of the animals with Fc-ectodomain fusions significantly increased the ability of draining lymph node T-cells to lyse target 4T1 tumor cells ex

vivo. It can be seen that this immuno-stimulatory effect is specific to 4T1 cells since the T-cells were not able to effectively lyse B16F10 melanoma cells (FIG. **9**C; maximal lysis of ~15% for B16F10 cells and ~80% for 4T1 cells). When administered at the same 5 mg/kg dose as the Fc-ectodomain fusions, the non-Fc-fused comparator molecule, T22d35, had no effect above saline. This is consistent with its lack of effect on tumor volume. Although the 1D11 antibody had no statistically significant effect on tumor volume (FIG. **9**A), it did increase the ability of lymph node T-cells to lyse 4T1 tumor cells.

Interestingly, with respect to the Fc-ectodomain fusions of this invention, the most potent constructs were the hIgG1FcΔK(CC)-T2m and hIgG2FcΔK(CC)-T2m constructs; both of these constructs containing two cysteines in the engineered hinge region. These constructs were more potent than the construct with one cysteine in the engineered hinge region, hIgG1FcΔK(C)-T2m, as well as being more potent than the full-size antibody-T2m construct, Cet-T2m. The difference in potency between constructs with one versus two hinge region cysteines may result from the construct with one cysteine having a lower relative stability. The lower potency of the full size antibody construct relative to the headless constructs with two hinge region cysteines may result from a difference in molecular weight, with the smaller constructs being able to penetrate the tumor microenvironment more effectively.

Example 7: In Vitro and In Vivo Studies Illustrating Enhanced Bone Localization of Constructs Containing a Deca-Aspartate Motif for Bone Targeting at the N-Terminus of the Fc Region

In vivo studies were carried out to investigate whether the addition of a 10 amino acid long poly-aspartate bone-localization motif (D10) to the N-terminus of the Fc region of constructs will promote their localization to bone. Optical imaging of D10-hIgG1 Fc-T2m fusions: Upon arrival, male Balb/c mice were housed 3 mice/cage. On the day of the experiment, animals were shaved dorsal and ventral and treated with the hair removal cream, NAIR®. Mice were injected with a single intravenous bolus of 10 mg/kg of two CF770 labeled constructs with a deca-aspartate motif for bone targeting (D10) at their N-termini (D10-hIgG1FcΔK(CC)-T2m, D10-GSL-hIgG1FcΔK(CC)-T2m) or with a control construct without the D10 motif (hIgG1FcΔK(CC)-T2m) and whole body bio-distribution followed using both in vivo and ex-vivo near infrared imaging. Imaging was conducted with a small-animal time-domain eXplore Optix pre-clinical imager MX3 (Advanced Research Technologies, ART) at various time points (prescan, 5 mins, 3 hr, 6 hr, 24 h, 48 h, 72 h, 96 h and 120 h).

The small animal time-domain eXplore Optix preclinical imagers consists of a 785-nm pulsed laser diode with a repetition frequency of 80 MHz and a time resolution of 12.5 ps light pulse was used for excitation. The fluorescence emission beyond 813 nm was collected by a highly sensitive time-correlated single photon counting system and detected through a fast photomultiplier tube. The data were recorded as temporal point-spread functions (TPSF) and the images were presented as fluorescence intensity maps using ART Optix Optiview analysis software 3.02.

For in vivo optical imaging, mice were first anesthetized using isofluorane (1.5-2%), positioned on the animal stage within a chamber which allows for gaseous anesthesia and maintenance of animal temperature at 36° C. The scanning of the mouse at each time point lasted up to 20 mins using a 2.5 mm step size and the mouse is placed back in its home cage between imaging time points.

At the end of the imaging protocol (120 hrs) animals were sacrificed by intracardiac perfusion using heparnized saline with deep anesthesia. The organs (brain, heart, lungs, liver, kidney, spleen and right and left leg bones) were imaged ex-vivo using a 1.0 mm step size using the eXplore Optix pre-clincal imager MX3.

Data analysis was done using eXplore Optix Optiview analysis software 3.02 (Advanced Research Technologies, Montreal, QC) to estimate the fluorescence total and average fluorescence intensity in region of interest containing the ex-vivo organs.

The results shown in FIGS. **10**A and B demonstrate that the fusion of the deca-aspartate D10 motif on the N-termini of the fusion constructs had no impact on their ability to neutralize TGF-β, i.e. the IC_{50} of the construct lacking the D10 motif (hIgG1FcΔK(CC)-T2m) was 3 nM, which is the same as the value determined in FIG. **4**C, while the IC_{50}s of the D10 containing constructs, D10-hIgG1FcΔK(CC)-T2m and D10-GSL-hIgG1FcΔK(CC)-T2m, were very similar at 4-5 nM. The results in FIGS. **10**A and B also indicate that labeling with the CF770 dye reduced the ability of the constructs to neutralize TGF-β by approximately 4-fold. Since dye conjugation occurs at lysine residues, and since it is know that lysines are at the binding interface between the Type II ectodomain and TGF-β, it is not entirely surprising that labeling reduced neutralization potency. In any case, since this is a comparative study of differences in in vivo localization promoted by the D10 peptide, it was felt that partially active constructs would be informative.

The results shown in FIGS. **10**C and D demonstrate that the addition of the D10 peptide to the N-termini of the constructs greatly enhanced bone localization. Images taken 120 h post-injection of the CF770 labeled fusions show a clear accumulation of the D10-fusions in the vertebrae. Further ex vivo imaging of the brain, heart, lungs, liver, kidneys, spleen, and the left and right legs 120 h post-injection confirmed the specific accumulation of the D10-fusions in the bones. The fluorescent signals observed in the kidneys and liver were similar for all fusions indicating that accumulation in these organs was not affected by the presence of the D10 sequence. These results indicate that the TGF-β neutralization activity of constructs may be increased within bone through the addition of the D10 peptide. This could result in more favourable dosing levels and schedules for the treatment of bone-related diseases, such as osteogenesis imperfecta, relative to that required for a similar construct without the D10 motif.

The embodiments and examples described herein are illustrative and are not meant to limit the scope of the invention as claimed. Variations of the foregoing embodiments, including alternatives, modifications and equivalents, are intended by the inventors to be encompassed by the claims. Furthermore, the discussed combination of features might not be necessary for the inventive solution.

LISTING OF SEQUENCES

SEQ ID NO:	Sequence	Description
1	APELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPA	Human IgG1 Fc region

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LISTING OF SEQUENCES

SEQ ID NO:	Sequence	Description
	PIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVKHE ALHNHYTQKSLSLSPGK	
2	APPVAGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTFRVVSVL TVVHQDWLNGKEYKCKVSNKGLPAP IEKTISKTKGQPREPQVYTLPPSRE EKTKNQVSLTCLVKGFYPSDISVEW ESNGQPENNYKTTPPMLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVKHEA LHNHYTQKSLSLSPGK	Human IgG2 Fc region
3	APELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVQFKWYVD GVEVHNAKTKPREEQYNSTFRVVSV LTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKTKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVE WESSGQPENNYNTTPPMLDSDGSFF LYSKLTVDKSRWQQGNIFSCSVMHE ALHNRFTQKSLSLSPGK	Human IgG3 Fc region
4	APEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFF LYSRLTVDKSRWQEGNVFSCSVKHE ALHNHYTQKSLSLSLGK	Human IgG4 Fc region
5	EPKSCDKTHTCPPCP	Human IgG1 hinge region
6	ERKCCVECPPCP	Human IgG2 hinge region
7	ELKTPLCDTTHTCPRCPEPKSCDTP PPCPRCPEPKSCDTPPPCPRCPEPK SCDTPPPCPRCP	Human IgG3 hinge region
8	ESKYGPPCPSCP	Human IgG4 hinge region
9	APELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVKHE ALHNHYTQKSLSLSPG	hIgG1FcΔK-AC Fc variant
10	PPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCS VKHEALHNHYTQKSLSLSPG	hIgG1FcΔK-C Fc variant
11	DKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYK	hIgG1FcΔK-CC Fc variant

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LISTING OF SEQUENCES

SEQ ID NO:	Sequence	Description
	CKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSP G	
12	EPKSSDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKS LSLSPG	hIgG1FcΔK-S Fc variant
13	EPKSSDKTHTCPPCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKS LSLSPG	hIgG1ΔK-SS Fc variant
14	EPKSSDKTHTSPPSPAPELLCGPSV FLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDCVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKS RWQQCNVFSCSVMHEALHNHYTQKS LSLSPC	hIgG1FcΔK-SSS Fc variant
15	APPVAGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTFRVVSVL TVVHQDWLNGKEYKCKVSNKGLPAP IEKTISKTKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDISVEW ESNGQPENNYKTTPPMLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPG	hIgG2FcΔK-AC Fc variant
16	PPCPAPPVACPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRV VSVLTVVHQDWLNGKEYKCKVSNKG LPAPIEKTISKTKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDI SVEWESNGQPENNYKTTPPMLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG	hIgG2FcΔK-C Fc variant
17	VECPPCPAPPVAGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVQ FNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQDWLNGKEYKCKVS NKGLPAPIEKTISKTKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYP SDISVEWESNGQPENNYKTTPPMLD SDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG	hIgG2FcΔK-CC Fc variant
18	ERKCCVECPPCPAPPVAGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHE DPEVQFNWYVDGVEVHNAKTKPREE	hIgG2Fc-CCCC Fc variant

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LISTING OF SEQUENCES

SEQ ID NO:	Sequence	Description
	QFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPR EPQVYTLPPSREEKTKNQVSLTCLV KGFYPSDISVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVKHEALHNHYTQKSLSLS PGK	
19	ERKSSVECPPCPAPPVAGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHE DPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPR EPQVYTLPPSREEKTKNQVSLTCLV KGFYPSDISVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVNHEALHNHYTQKSLSLS PG	hIgG2FcΔK-SS Fc variant
20	ERKSSVESPPCPAPPVAGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHE DPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPR EPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDISVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLS PG	hIgG2FcΔK-SSS Fc variant
21	ERKSSVESPPSPAPPVAGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHE DPEVQFNWYVDGVEVHNAKTKPREE QFNSTFRVVSVLTVVHQDWLNGKEY KCKVSNKGLPAPIEKTISKTKGQPR EPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDISVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLS PG	hIgG2FcΔK-SSSS Fc variant
22	APELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVQFKWYVD GVEVHNAKTKPREEQYNSTFRVVSV LTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKTKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVE WESSGQPENNYNTTPPMLDSDGSFF LYSKLTVDKSRWQQGNIFSCSVMHE ALHNRFTQKSLSLSPG	hIgG3FcΔK-AC Fc variant
23	PRCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVQFK WYVDGVEVHNAKTKPREEQYNSTFR VVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKTKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSD IAVEWESSGQPENNYNTTPPMLDSD GSFFLYSKLTVDKSRWQQGNIFSCS VKHEALHNRFTQKSLSLSPG	hIgG3FcΔK-C Fc variant
24	DTPPPCPRCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHED PEVQFKWYVDGVEVHNAKTKPREEQ YNSTFRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKTKCQPRE PQVYTLPPSREEMTKNQVSLTCLVK CFYPSDIAVEWESSGQPENNYNTTP PMLDSDCSFFLYSKLTVDKSRWQQG NIFSCSVMHEALHNRFTQKSLSLSP G	hIgG3FcΔK-CC Fc variant

-continued

LISTING OF SEQUENCES

SEQ ID NO:	Sequence	Description
25	EPKSSDTPPPCPRCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVQFKWYVDGVEVHNAKTK PREEQYNSTFRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKTK GQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESSGQPENN YNTTPPMLDSDGSFFLYSKLTVDKS RWQQGNIFSCSVMHEALHNRFTQKS LSLSPG	hIgG3FcΔK-S Fc variant
26	EPKSSDTPPPSPRCPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVQFKWYVDCVEVHNAKTK PREEQYNSTFRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKTK GQPREPQVYTLPPSREEMTKNQVSL TCLVKCFYPSDIAVEWESSGQPENN YNTTPPMLDSDGSFFLYSKLTVDKS RWQQGNIFSCSVMHEALHNRFTQKS LSLSPG	hIgG3FcΔK-SS Fc variant
27	EPKSSDTPPPSPRSPAPELLGGPSV FLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVQFKWYVDGVEVHNAKTK PREEQYNSTFRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKTK GQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESSGQPENN YNTTPPMLDSDGSFFLYSKLTVDKS RWQQGNIFSCSVMHEALHNRFTQKS LSLSPG	hIgG3FcΔK-SSS Fc variant
28	APEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKCQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFF LYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLG	hIgG4FcΔK-AC Fc variant
29	PSCPAPEFLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLSLG	hIgG4FcΔK-C Fc variant
30	ESKYGPPCPSCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLG	hIgG4FcΔK-CC Fc variant
31	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQ	hIgG4FcΔK-CC-228P Fc variant

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SEQ ID NO:	Sequence	Description
	EGNVFSCSVMHEALHNHYTQKSLSL SLG	
32	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLG	hIgG4FcΔK-CC-228P-409K Fc variant
33	ESKYCPPSPSCPAPEFLCCPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLG	hIgG4FcΔK-S Fc variant
34	ESKYGPPSPSSPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDCVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLG	hIgG4FcΔK-SS Fc variant
35	QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPCETFFMCSCSSDECNDNII F	TβRII-ED structured domain
36	IPPHVQKSVNNDMIVTDNNGAVKFP	TβRII-ED N-term unstructured region and natural linker
37	IPPHVQKSDVEMEAQKDEIICPSCN RTAHPLRHINNDMIVTDNNCAVKFP	TβRIIb-ED N-term unstructured region and natural linker
38	IPPHVQKSDVEMEAQKDEIIAPSAN RTAHPLRHINNDMIVTDNNGAVKFP	TβRIIb-ED Cys-mutated N-term unstructured region and natural linker
39	SEEYNTSNPD	TβRII-ED C-term unstructured region and natural linker
40	SEEYNTSNPDIPPHVQKSVNNDMIV TDNNGAVKFP	TβRII-ED natural linker
41	SEEYNTSNPDIPPHVQKSDVEMEAQ KDEIICPSCNRTAHPLRHINNDMIV TDNNGAVKFP	TβRIIb-ED natural linker
42	SEEYNTSNPDIPPHVQKSDVEMEAQ KDEIIAPSANRTAHPLRHINNDMIV TDNNGAVKFP	TβRIIb-ED Cys-mutated linker

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LISTING OF SEQUENCES

SEQ ID NO:	Sequence	Description
43	IPPHVQKSVNNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPD	TβRII-ED monomer, also termed T2 or T2m
44	IPPHVQKSDVEMEAQKDEIICPSCN RTAHPLRHINNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPD	TpbRIIb-ED monomer, also termed T2b
45	IPPHVQKSDVEMEAQKDEIIAPSAN RTAHPLRHINNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPD	TβRIIb-ED monomer Cys-mutated in the linker region, also termed $T2b^{AA}$
46	IPPHVQKSVNNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPDIPPHVQKSVNNDMI VTDNNGAVKFPQLCKFCDVRFSTCD NQKSCMSNCSITSICEKPQEVCVAV WRKNDENITLETVCHDPKLPYHDFI LEDAASPKCIMKEKKKPGETFFMCS CSSDECNDNIIFSEEYNTSNPD	TβRII-ED dimer, also termed T2-T2 or T22d35
47	IPPHVQKSDVEMEAQKDEIICPSCN RTAHPLRHINNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPDIPPHVQKSDVEMEA QKDEIICPSCNRTAHPLRHINNDMI VTDNNGAVKFPQLCKFCDVRFSTCD NQKSCMSNCSITSICEKPQEVCVAV WRKNDENITLETVCHDPKLPYHDFI LEDAASPKCIMKEKKKPGETFFMCS CSSDECNDNIIFSEEYNTSNPD	TβRIIb-ED dimer, also termed T2-T2b
48	IPPHVQKSDVEMEAQKDEIICPSCN RTAHPLRHINNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPDIPPHVQKSDVEMEA QKDEIIAPSANRTAHPLRHINNDMI VTDNNGAVKFPQLCKFCDVRFSTCD NQKSCMSNCSITSICEKPQEVCVAV WRKNDENITLETVCHDPKLPYHDFI LEDAASPKCIMKEKKKPGETFFMCS CSSDECNDNIIFSEEYNTSNPD	TβRIIb-ED dimer Cys-mutated in the linker region, also termed T2-$T2b^{AA}$
49	IPPHVQKSVNNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPDIPPHVQKSVNNDMI VTDNNGAVKFPQLCKFCDVRFSTCD NQKSCMSNCSITSICEKPQEVCVAV WRKNDENITLETVCHDPKLPYHDFI	TβRII-ED trimer, also termed T2-T2

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SEQ ID NO:	Sequence	Description
	LEDAASPKCIMKEKKKPGETFFMCS CSSDECNDNIIFSEEYNTSNPDIPP HVQKSVNNDMIVTDNNGAVKFPQLC KFCDVRFSTCDNQKSCMSNCSITSI CEKPQEVCVAVWRKNDENITLETVC HDPKLPYHDFILEDAASPKCIMKEK KKPGETFFMCSCSSDECNDNIIFSE EYNTSNPD	
50	IPPHVQKSVNNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPDIPPHVQKSDVEMEA QKDEIICPSCNRTAHPLRHINNDMI VTDNNGAVKFPQLCKFCDVRFSTCD NQKSCMSNCSITSICEKPQEVCVAV WRKNDENITLETVCHDPKLPYHDFI LEDAASPKCIMKEKKKPGETFFMCS CSSDECNDNIIFSEEYNTSNPDIPP HVQKSDVEMEAQKDEIICPSCNRTA HPLRHINNDMIVTDNNGAVKFPQLC KFCDVRFSTCDNQKSCMSNCSITSI CEKPQEVCVAVWRKNDENITLETVC HDPKLPYHDFILEDAASPKCIMKEK KKPGETFFMCSCSSDECNDNIIFSE EYNTSNPD	TβRIIb-ED trimer, also termed T2-T2b-T2b
51	IPPHVQKSVNNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPDIPPHVQKSDVEMEA QKDEIIAPSANRTAHPLRHINNDMI VTDNNGAVKFPQLCKFCDVRFSTCD NQKSCMSNCSITSICEKPQEVCVAV WRKNDENITLETVCHDPKLPYHDFI LEDAASPKCIMKEKKKPGETFFMCS CSSDECNDNIIFSEEYNTSNPDIPP HVQKSDVEMEAQKDEIIAPSANRTA HPLRHINNDMIVTDNNGAVKFPQLC KFCDVRFSTCDNQKSCMSNCSITSI CEKPQEVCVAVWRKNDENITLETVC HDPKLPYHDFILEDAASPKCIMKEK KKPGETFFMCSCSSDECNDNIIFSE EYNTSNPD	TβRIIb-ED trimer Cys-mutated in the linker regions, also termed T2-T2b^{AA}-T2b^{AA}
52	ALQCFCHLCTKDNFTCVTDGLCFVS VTETTDKVIHNSMCIAEIDLIPRDR PFVCAPSSKTGSVTTTYCCNQDHCN KIEL	TβRI-ED structured domain
53	AALLPGAT	TβRI-ED N-term unstructured region and natural linker
54	PTTVKSSPGLGPVE	TβRI-ED C-term unstructured region and natural linker
55	PTTVKSSPGLGPVEAALLPGAT	TβRI-ED natural linker
56	AALLPGATALQCFCHLCTKDNFTCV TDGLCFVSVTETTDKVIHNSMCIAE IDLIPRDRPFVCAPSSKTGSVTTTY CCNQDHCNKIELPTTVKSSPGLGPV E	TβRI-ED monomer, also termed T1 or T1m

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LISTING OF SEQUENCES

SEQ ID NO:	Sequence	Description
57	AALLPGATALQCFCHLCTKDNFTCV TDGLCFVSVTETTDKVIHNSMCIAE IDLIPRDRPFVCAPSSKTGSVTTTY CCNQDHCNKIELPTTVKSSPGLGPV EAALLPGATALQCFCHLCTKDNFTC VTDGLCFVSVTETTDKVIHNSMCIA EIDLIPRDRPFVCAPSSKTGSVTTT YCCNQDHCNKIELPTTVKSSPGLGP VE	TβRI-ED dimer, also termed T1-T1
58	PTTVKSSPGLGPVEIPPHVQKSVNN DMIVTDNNGAVKFP	TβRI-TβRII-ED natural linker
59	PTTVKSSPGLGPVEIPPHVQKSDVE MEAQKDEIICPSCNRTAHPLRHINN DMIVTDNNGAVKFP	TβRI-TβRIIb-ED natural linker
60	SEEYNTSNPDAALLPGAT	TβRII-TβRI-ED natural linker
61	AALLPGATALQCFCHLCTKDNFTCV TDGLCFVSVTETTDKVIHNSMCIAE IDLIPRDRPFVCAPSSKTGSVTTTY CCNQDHCNKIELPTTVKSSPGLGPV EIPPHVQKSVNNDMIVTDNNGAVKF PQLCKFCDVRFSTCDNQKSCMSNCS ITSICEKPQEVCVAVWRKNDENITL ETVCHDPKLPYHDFILEDAASPKCI MKEKKKPGETFFMCSCSSDECNDNI IFSEEYNTSNPD	TβRI-TβRII-ED dimer T1-T2
62	AALLPGATALQCFCHLCTKDNFTCV TDGLCFVSVTETTDKVIHNSMCIAE IDLIPRDRPFVCAPSSKTGSVTTTY CCNQDHCNKIELPTTVKSSPGLCPV EIPPHVQKSDVEMEAQKDEIICPSC NRTAHPLRHINNDMIVTDNNGAVKF PQLCKFCDVRFSTCDNQKSCMSNCS ITSICEKPQEVCVAVWRKNDENITL ETVCHDPKLPYHDFILEDAASPKCI MKEKKKPGETFFMCSCSSDECNDNI IFSEEYNTSNPD	TβRI-TβRII-ED dimer T1-T2b
63	IPPHVQKSVNNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPDAALLPGATALQCFC HLCTKDNFTCVTDGLCFVSVTETTD KVIHNSMCIAEIDLIPRDRPFVCAP SSKTGSVTTTYCCNQDHCNKIELPT TVKSSPGLGPVE	TβRI-TβRII-ED dimer T2-T1
64	AALLPGATALQCFCHLCTKDNFTCV TDGLCFVSVTETTDKVIHNSMCIAE IDLIPRDRPFVCAPSSKTGSVTTTY CCNQDHCNKIELPTTVKSSPGLGPV EIPPHVQKSVNNDMIVTDNNGAVKF PQLCKFCDVRFSTCDNQKSCMSNCS ITSICEKPQEVCVAVWRKNDENITL ETVCHDPKLPYHDFILEDAASPKCI MKEKKKPGETFFMCSCSSDECNDNI IFSEEYNTSNPDIPPHVQKSVNNDM IVTDNNGAVKFPQLCKFCDVRFSTC DNQKSCMSNCSITSICEKPQEVCVA VWRKNDENITLETVCHDPKLPYHDF ILEDAASPKCIMKEKKKPGETFFMC SCSSDECNDNIIFSEEYNTSNPD	TβRI-TβRII-ED trimer T1-T2-T2
65	AALLPGATALQCFCHLCTKDNFTCV TDGLCFVSVTETTDKVIHNSMCIAE IDLIPRDRPFVCAPSSKTGSVTTTY	TβRI-TβRII-ED trimer T1-T2-T2b

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LISTING OF SEQUENCES

SEQ ID NO:	Sequence	Description
	CCNQDHCNKIELPTTVKSSPGLGPV EIPPHVQKSVNNDMIVTDNNGAVKF PQLCKFCDVRFSTCDNQKSCMSNCS ITSICEKPQEVCVAVWRKNDENITL ETVCHDPKLPYHDFILEDAASPKCI MKEKKKPGETFFMCSCSSDECNDNI IFSEEYNTSNPDIPPHVQKSDVEME AQKDEIICPSCNRTAHPLRHINNDM IVTDNNGAVKFPQLCKFCDVRFSTC DNQKSCMSNCSITSICEKPQEVCVA VWRKNDENITLETVCHDPKLPYHDF ILEDAASPKCIMKEKKKPGETFFMC SCSSDECNDNIIFSEEYNTSNPD	
66	AALLPGATALQCFCHLCTKDNFTCV TDGLCFVSVTETTDKVIHNSMCIAE IDLIPRDRPFVCAPSSKTGSVTTTY CCNQDHCNKIELPTTVKSSPGLGPV EIPPHVQKSDVEMEAQKDEIICPSC NRTAHPLRHINNDMIVTDNNGAVKF PQLCKFCDVRFSTCDNQKSCMSNCS ITSICEKPQEVCVAVWRKNDENITL ETVCHDPKLPYHDFILEDAASPKCI MKEKKKPGETFFMCSCSSDECNDNI IFSEEYNTSNPDIPPHVQKSDVEME AQKDEIIAPSANRTAHPLRHINNDM IVTDNNGAVKFPQLCKFCDVRFSTC DNQKSCMSNCSITSICEKPQEVCVA VWRKNDENITLETVCHDPKLPYHDF ILEDAASPKCIMKEKKKPGETFFMC SCSSDECNDNIIFSEEYNTSNPD	TβRI-TβRII-ED trimer T1-T2-T2b^{AA}
67	IPPHVQKSVNNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPDIPPHVQKSVNNDMI VTDNNGAVKFPQLCKFCDVRFSTCD NQKSCMSNCSITSICEKPQEVCVAV WRKNDENITLETVCHDPKLPYHDFI LEDAASPKCIMKEKKKPGETFFMCS CSSDECNDNIIFSEEYNTSNPDAAL LPGATALQCFCHLCTKDNFTCVTDG LCFVSVTETTDKVIHNSMCIAEIDL IPRDRPFVCAPSSKTGSVTTTYCCN QDHCNKIELPTTVKSSPGLGPVE	TβRI-TβRII-ED trimer T2-T2-T1
68	IPPHVQKSVNNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPDIPPHVQKSDVEMEA QKDEIIAPSANRTAHPLRHINNDMI VTDNNGAVKFPQLCKFCDVRFSTCD NQKSCMSNCSITSICEKPQEVCVAV WRKNDENITLETVCHDPKLPYHDFI LEDAASPKCIMKEKKKPGETFFMCS CSSDECNDNIIFSEEYNTSNPDAAL LPGATALQCFCHLCTKDNFTCVTDG LCFVSVTETTDKVIHNSMCIAEIDL IPRDRPFVCAPSSKTCSVTTTYCCN QDHCNKIELPTTVKSSPGLGPVE	TβRI-TβRII-ED trimer T2-T2b^{AA}-T1
69	TLPFLKCYCSGHCPDDAINNTCITN GHCFAIIEEDDQGETTLASGCMKYE GSDFQCKDSPKAQLRRTIECCRTNL CNQYLQPTLP	BMPRIa-ED structured domain
70	QNLDSMLHGTGMKSDSDQKKSENGV TLAPED	BMPRIa-ED N-term unstructured region and natural linker
71	PWIGPFFDGSIR	BMPRIa-ED C-term unstructured region and natural linker
72	PWIGPFFDCSIRQNLDSMLHGTGMK SDSDQKKSENGVTLAPED	BMPRIa-ED natural linker
73	QNLDSMLHGTGMKSDSDQKKSENGV TLAPEDTLPFLKCYCSGHCPDDAIN NTCITNGHCFAIIEEDDQGETTLAS GCMKYEGSDFQCKDSPKAQLRRTIE CCRTNLCNQYLQPTLPPVVIGPFFD GSIR	BMPRIa-ED monomer
74	QNLDSMLHGTGMKSDSDQKKSENGV TLAPEDTLPFLKCYCSGHCPDDAIN NTCITNGHCFAIIEEDDQGETTLAS CCMKYEGSDFQCKDSPKAQLRRTIE CCRTNLCNQYLQPTLPPVVIGPFFD GSIRQNLDSMLHGTGMKSDSDQKKS ENGVTLAPEDTLPFLKCYCSGHCPD DAINNTCITNCHCFAIIEEDDQCET TLASGCMKYEGSDFQCKDSPKAQLR RTIECCRTNLCNQYLQPTLPPWIGP FFDGSIR	BMPRIa-ED dimer
75	TQECLFFNANWEKDRTNQTGVEPCY GDKDKRRHCFATWKNISGSIEIVKQ GCWLDDINCYDRTDCVEKKDSPEVY FCCCEGNMCNEKFSYFP	ActRila-ED structured domain
76	AILGRSE	ActRIIa-ED N-term unstructured region and natural linker
77	EMEVTQPTSNPVTPKPPYYNI	ActRIIa-ED C-term unstructured region and natural linker
78	EMEVTQPTSNPVTPKPPYYNIAILG RSE	ActRIIa-ED natural linker
79	AILGRSETQECLFFNANWEKDRTNQ TGVEPCYGDKDKRRHCFATWKNISG SIEIVKQGCWLDDINCYDRTDCVEK KDSPEVYFCCCEGNMCNEKFSYFPE MEVTQPTSNPVTPKPPYYNI	ActRIIa-ED monomer
80	AILGRSETQECLFFNANWEKDRTNQ TGVEPCYCDKDKRRHCFATWKNISG SIEIVKQGCWLDDINCYDRTDCVEK KDSPEVYFCCCEGNMCNEKFSYFPE MEVTQPTSNPVTPKPPYYNIAILGR SETQECLFFNANWEKDRTNQTGVEP CYGDKDKRRHCFATWKNISGSIEIV KQGCWLDDINCYDRTDCVEKKDSPE VYFCCCEGNMCNEKFSYFPEMEVTQ PTSNPVTPKPPYYNI	ActRIIa-ED dimer
81	RECIYYNANWELERTNQSGLERCEG EQDKRLHCYASWRNSSGTIELVKKG CWLDDFNCYDRQECVATEENPQVYF CCCEGNFCNERFTHLP	ActRIIb-ED structured domain

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SEQ ID NO:	Sequence	Description
82	SGRGEAET	ActRIIb-ED N-term unstructured region and natural linker
83	EAGGPEVTYEPPPTAPT	ActRIIb-ED C-term unstructured region and natural linker
84	EAGGPEVTYEPPPTAPTSGRGEAET	ActRIIb-ED natural linker
85	SGRGEAETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCECNFCNERFTHLPEAGGPEVTYEPPPTAPT	ActRIIb-ED monomer
86	SGRGEAETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPTSGRGEAETRECIYYNANWELERTNQSGLERCEGEQDKRLHCYASWRNSSGTIELVKKGCWLDDFNCYDRQECVATEENPQVYFCCCEGNFCNERFTHLPEAGGPEVTYEPPPTAPT	ActRIIb-ED dimer
87	EMEVTQPTSNPVTPKPPYYNIQNLDSMLHGTCMKSDSDQKKSENCVTLAPED	ActRIIa-BMPRIa-ED natural linker
88	AILGRSETQECLFFNANWEKDRTNQTGVEPCYGDKDKRRHCFATWKNISGSIEIVKQGCWLDDINCYDRTDCVEKKDSPEVYFCCCEGNMCNEKFSYFPEMEVTQPTSNPVTPKPPYYNIQNLDSMLHGTGMKSDSDQKKSENGVTLAPEDTLPFLKCYCSGHCPDDAINNTCITNGHCFAIIEEDDQGETTLASGCMKYEGSDFQCKDSPKAQLRRTIECCRTNLCNQYLQPTLPPWIGPFFDGSIR	ActRIIa-BMPRIa-ED dimer
89	MDWTWRILFLVAAATCTHA	Signal peptide
90	MVLQTQVFISLLLWISGAYG	Signal peptide
91	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGIPPHVQKSVNNDKIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCKSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD	hIgG1FcΔK-AC-T2m fusion
92	PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVKHEALHNHYTQKSLSLSPGIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD	hIgG1FcΔK-C-T2m fusion
93	DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD	hIgG1FcΔK-CC-T2m fusion
94	APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVKHEALHNHYTQKSLSLSPGIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD	hIgG2FcΔK-AC-T2m fusion
95	PPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCWVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD	hIgG2FcΔK-C-T2m fusion
96	APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD	hIgG2FcΔK-CC-T2m fusion

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SEQ ID NO:	Sequence	Description
97	MDWTWRILFLVAAATGTHAERKCCV ECPPCPAPPVAGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTF RVVSVLTVVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYT LPPSREEMTKNQVSLTCLVKCFYPS DISVEWESNCQPENNYKTTPPMLDS DCSFFLYSKLTVDKSRWQQGNVFSC SVKHEALHNHYTQKSLSLSPGKIPP HVQKSVNNDMIVTDNNGAVKFPQLC KFCDVRFSTCDNQKSCKSNCSITSI CEKPQEVCVAVWRKNDENITLETVC HDPKLPYHDFILEDAASPKCIMKEK KKPGETFFMCSCSSDECNDNIIFSE EYNTSNPD	hIgG2Fc-CCCC-T2 fusion, also termed Fc-T2m
98	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLGIPPHVQKSVNNDMIVTDNNCAV KFPQLCKFCDVRFSTCDNQKSCMSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPD	hIgG4FcΔK-CC-228P-T2m fusion
99	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLGIPPHVQKSVNNDMIVTDNNGAV KFPQLCKFCDVRFSTCDNQKSCKSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPD	hIgG4FcΔK-CC-228P-409K-T2m fusion
100	PPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCS VKHEALHNHYTQKSLSLSPGIPPHV QKSVNNDMIVTDNNGAVKFPQLCKF CDVRFSTCDNQKSCMSNCSITSICE KPQEVCVAVWRKNDENITLETVCHD PKLPYHDFILEDAASPKCIMKEKKK PGETFFMCSCSSDECNDNIIFSEEY NTSNPDIPPHVQKSVNNDMIVTDNN GAVKFPQLCKFCDVRFSTCDNQKSC MSNCSITSICEKPQEVCVAVWRKND ENITLETVCHDPKLPYHDFILEDAA SPKCIMKEKKKPGETFFMCSCSSDE CNDNIIFSEEYNTSNPD	hIgG1FcΔK-C-T22d35 fusion
101	DKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDCVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNCKEYK CKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSP GIPPHVQKSVNNDMIVTDNNGAVKF PQLCKFCDVRFSTCDNQKSCMSNCS ITSICEKPQEVCVAVWRKNDENITL ETVCHDPKLPYHDFILEDAASPKCI MKEKKKPGETFFMCSCSSDECNDNI IFSEEYNTSNPDIPPHVQKSVNNDM IVTDNNGAVKFPQLCKFCDVRFSTC DNQKSCMSNCSITSICEKPQEVCVA VWRKNDENITLETVCHDPKLPYHDF ILEDAASPKCIMKEKKKPGETFFMC SCSSDECNDNIIFSEEYNTSNPD	hIgG1FcΔK-CC-T22d35 fusion
102	VECPPCPAPPVAGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVQ FNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQDWLNGKEYKCKVS NKGLPAPIEKTISKTKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYP SDISVEWESNGQPENNYKTTPPMLD SDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGIPP HVQKSVNNDMIVTDNNGAVKFPQLC KFCDVRFSTCDNQKSCMSNCSITSI CEKPQEVCVAVWRKNDENITLETVC HDPKLPYHDFILEDAASPKCIMKEK KKPGETFFMCSCSSDECNDNIIFSE EYNTSNPDIPPHVQKSVNNDMIVTD NNGAVKFPQLCKFCDVRFSTCDNQK SCMSNCSITSICEKPQEVCVAVWRK NDENITLETVCHDPKLPYHDFILED AASPKCIMKEKKKPGETFFMCSCSS DECNDNIIFSEEYNTSNPD	hIgG2FcΔK-CC-T22d35 fusion
103	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLGIPPHVQKSVNNDMIVTDNNGAV KFPQLCKFCDVRFSTCDNQKSCMSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPDIPPHVQKSVNN DMIVTDNNGAVKFPQLCKFCDVRFS TCDNQKSCMSNCSITSICEKPQEVC VAVWRKNDENITLETVCHDPKLPYH DFILEDAASPKCIMKEKKKPGETFF MCSCSSDECNDNIIFSEEYNTSNPD	hIgG4FcΔK-CC-228P-T22d35 fusion
104	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLGIPPHVQKSVNNDMIVTDNNGAV KFPQLCKFCDVRFSTCDNQKSCMSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK	hIgG4FcΔK-CC-228P-409K-T22d35 fusion

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SEQ ID NO:	Sequence	Description
	CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPDIPPHVQKSVNN DMIVTDNNGAVKFPQLCKFCDVRFS TCDNQKSCMSNCSITSICEKPQEVC VAVWRKNDENITLETVCHDPKLPYH DFILEDAASPKCIMKEKKKPGETFF MCSCSSDECNDNIIFSEEYNTSNPD	
105	MDWTWRILFLVAAATGTHAERKCCV ECPPCPAPPVAGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTF RVVSVLTVVHQDWLNGKEYKCKVSN KGLPAPIEKTISKTKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPS DISVEWESNGQPENNYKTTPPMLDS DGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGKIPP HVQKSVNNDMIVTDNNGAVKFPQLC KFCDVRFSTCDNQKSCMSNCSITSI CEKPQEVCVAVWRKNDENITLETVC HDPKLPYHDFILEDAASPKCIMKEK KKPGETFFMCSCSSDECNDNIIFSE EYNTSNPDIPPHVQKSVNNDMIVTD NNGAVKFPQLCKFCDVRFSTCDNQK SCMSNCSITSICEKPQEVCVAVWRK NDENITLETVCHDPKLPYHDFILED AASPKCIMKEKKKPGETFFMCSCSS DECNDNIIFSEEYNTSNPD	hIgG2Fc-CCCC-T22d35 fusion, also termed Fc-T22d35
106	PPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCWVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGIPPHVQ KSVNNDMIVTDNNGAVKFPQLCKFC DVRFSTCDNQKSCMSNCSITSICEK PQEVCVAVWRKNDENITLETVCHDP KLPYHDFILEDAASPKCIMKEKKKP GETFFMCSCSSDECNDNIIFSEEYN TSNPDIPPHVQKSDVEMEAQKDEII APSANRTAHPLRHINNDMIVTDNNC AVKFPQLCKFCDVRFSTCDNQKSCM SNCSITSICEKPQEVCVAVWRKNDE NITLETVCHDPKLPYHDFILEDAAS PKCIMKEKKKPGETFFMCSCSSDEC NDNIIFSEEYNTSNPD	hIgG1FcΔK-C-T2-T2b^{AA} fusion
107	DKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSP GIPPHVQKSVNNDMIVTDNNGAVKF PQLCKFCDVRFSTCDNQKSCMSNCS ITSICEKPQEVCVAVWRKNDENITL ETVCHDPKLPYHDFILEDAASPKCI MKEKKKPGETFFMCSCSSDECNDNI IFSEEYNTSNPDIPPHVQKSDVEME AQKDEIIAPSANRTAHPLRHINNDM IVTDNNGAVKFPQLCKFCDVRFSTC DNQKSCMSNCSITSICEKPQEVCVA VWRKNDENITLETVCHDPKLPYHDF ILEDAASPKCIMKEKKKPGETFFMC SCSSDECNDNIIFSEEYNTSNPD	hIgG1FcΔK-CC-TP-TPb+ fusion

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SEQ ID NO:	Sequence	Description
108	VECPPCPAPPVAGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVQ FNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQDWLNGKEYKCKVS NKGLPAPIEKTISKTKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYP SDISVEWESNGQPENNYKTTPPMLD SDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGIPP HVQKSVNNDMIVTDNNGAVKFPQLC KFCDVRFSTCDNQKSCMSNCSITSI CEKPQEVCVAVWRKNDENITLETVC HDPKLPYHDFILEDAASPKCIMKEK KKPGETFFMCSCSSDECNDNIIFSE EYNTSNPDIPPHVQKSDVEMEAQKD EIIAPSANRTAHPLRHINNDMIVTD NNGAVKFPQLCKFCDVRFSTCDNQK SCMSNCSITSICEKPQEVCVAVWRK NDENITLETVCHDPKLPYHDFILED AASPKCIMKEKKKPGETFFMCSCSS DECNDNIIFSEEYNTSNPD	hIgG2FcΔK-CC-T2-T2b^{AA} fusion
109	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLGIPPHVQKSVNNDMIVTDNNGAV KFPQLCKFCDVRFSTCDNQKSCMSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPDIPPHVQKSDVE MEAQKDEIIAPSANRTAHPLRHINN DMIVTDNNGAVKFPQLCKFCDVRFS TCDNQKSCMSNCSITSICEKPQEVC VAVWRKNDENITLETVCHDPKLPYH DFILEDAASPKCIMKEKKKPGETFF MCSCSSDECNDNIIFSEEYNTSNPD	hIgG4FcΔK-CC-228P-T2-T2b^{AA} fusion
110	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLGIPPHVQKSVNNDMIVTDNNGAV KFPQLCKFCDVRFSTCDNQKSCMSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPDIPPHVQKSDVE MEAQKDEIIAPSANRTAHPLRHINN DMIVTDNNGAVKFPQLCKFCDVRFS TCDNQKSCMSNCSITSICEKPQEVC VAVWRKNDENITLETVCHDPKLPYH DFILEDAASPKCIMKEKKKPGETFF MCSCSSDECNDNIIFSEEYNTSNPD	hIgG4FcΔK-CC-228P-409K-T2-T2b^{AA} fusion
111	PPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFYPSD	hIgG1FcΔK-C-T2-T2-T2 fusion

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SEQ ID NO:	Sequence	Description
	IAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGIPPHV QKSVNNDMIVTDNNGAVKFPQLCKF CDVRFSTCDNQKSCMSNCSITSICE KPQEVCVAVWRKNDENITLETVCHD PKLPYHDFILEDAASPKCIMKEKKK PGETFFMCSCSSDECNDNIIFSEEY NTSNPDIPPHVQKSVNNDMIVTDNN GAVKFPQLCKFCDVRFSTCDNQKSC MSNCSITSICEKPQEVCVAVWRKND ENITLETVCHDPKLPYHDFILEDAA SPKCIMKEKKKPGETFFMCSCSSDE CNDNIIFSEEYNTSNPDIPPHVQKS VNNDMIVTDNNGAVKFPQLCKFCDV RFSTCDNQKSCMSNCSITSICEKPQ EVCVAVWRKNDENITLETVCHDPKL PYHDFILEDAASPKCIMKEKKKPGE TFFMCSCSSDECNDNIIFSEEYNTS NPD	
112	DKTHTCPPCPAPELLGGPSVFLFPP KPKDTLKISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSP GIPPHVQKSVNNDMIVTDNNGAVKF PQLCKFCDVRFSTCDNQKSCMSNCS ITSICEKPQEVCVAVWRKNDENITL ETVCHDPKLPYHDFILEDAASPKCI MKEKKKPGETFFMCSCSSDECNDNI IFSEEYNTSNPDIPPHVQKSVNNDM IVTDNNGAVKFPQLCKFCDVRFSTC DNQKSCMSNCSITSICEKPQEVCVA VWRKNDENITLETVCHDPKLPYHDF ILEDAASPKCIMKEKKKPGETFFMC SCSSDECNDNIIFSEEYNTSNPDIP PHVQKSVNNDMIVTDNNGAVKFPQL CKFCDVRFSTCDNQKSCMSNCSITS ICEKPQEVCVAVWRKNDENITLETV CHDPKLPYHDFILEDAASPKCIMKE KKKPGETFFMCSCSSDECNDNIIFS EEYNTSNPD	hIgG1FcΔK-CC-T2-T2-T2 fusion
113	VECPPCPAPPVAGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVQ FNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQDWLNGKEYKCKVS NKGLPAPIEKTISKTKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYP SDISVEWESNGQPENNYKTTPPMLD SDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGIPP HVQKSVNNDMIVTDNNGAVKFPQLC KFCDVRFSTCDNQKSCMSNCSITSI CEKPQEVCVAVWRKNDENITLETVC HDPKLPYHDFILEDAASPKCIMKEK KKPGETFFMCSCSSDECNDNIIFSE EYNTSNPDIPPHVQKSVNNDMIVTD NNGAVKFPQLCKFCDVRFSTCDNQK SCMSNCSITSICEKPQEVCVAVWRK NDENITLETVCHDPKLPYHDFILED AASPKCIMKEKKKPGETFFMCSCSS DECNDNIIFSEEYNTSNPDIPPHVQ KSVNNDMIVTDNNGAVKFPQLCKFC DVRFSTCDNQKSCMSNCSITSICEK PQEVCVAVWRKNDENITLETVCHDP	hIgG2FcΔK-CC-T2-T2-T2 fusion

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SEQ ID NO:	Sequence	Description
	KLPYHDFILEDAASPKCIMKEKKKP GETFFMCSCSSDECNDNIIFSEEYN TSNPD	
114	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLGIPPHVQKSVNNDMIVTDNNGAV KFPQLCKFCDVRFSTCDNQKSCMSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPDIPPHVQKSVNN DMIVTDNNGAVKFPQLCKFCDVRFS TCDNQKSCMSNCSITSICEKPQEVC VAVWRKNDENITLETVCHDPKLPYH DFILEDAASPKCIMKEKKKPGETFF MCSCSSDECNDNIIFSEEYNTSNPD IPPHVQKSVNNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPD	hIgG4FcΔK-CC-228P-T2-T2-T2 fusion
115	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLGIPPHVQKSVNNDMIVTDNNGAV KFPQLCKFCDVRFSTCDNQKSCMSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPDIPPHVQKSVNN DMIVTDNNGAVKFPQLCKFCDVRFS TCDNQKSCMSNCSITSICEKPQEVC VAVWRKNDENITLETVCHDPKLPYH DFILEDAASPKCIMKEKKKPGETFF MCSCSSDECNDNIIFSEEYNTSNPD IPPHVQKSVNNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPD	hIgG4FcΔK-CC-228P-409K-T2-T2-T2 fusion
116	PPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGIPPHV QKSVNNDMIVTDNNGAVKFPQLCKF CDVRFSTCDNQKSCMSNCSITSICE KPQEVCVAVWRKNDENITLETVCHD PKLPYHDFILEDAASPKCIMKEKKK PGETFFMCSCSSDECNDNIIFSEEY NTSNPDIPPHVQKSDVEMEAQKDEI	hIgG1FcΔK-C-T2-T2b^{AA}-T2b^{AA} fusion

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SEQ ID NO:	Sequence	Description
	IAPSANRTAHPLRHINNDMIVTDNN GAVKFPQLCKFCDVRFSTCDNQKSC MSNCSITSICEKPQEVCVAVWRKND ENITLETVCHDPKLPYHDFILEDAA SPKCIMKEKKKPGETFFMCSCSSDE CNDNIIFSEEYNTSNPDIPPHVQKS DVEMEAQKDEIIAPSANRTAHPLRH INNDMIVTDNNGAVKFPQLCKFCDV RFSTCDNQKSCMSNCSITSICEKPQ EVCVAVWRKNDENITLETVCHDPKL PYHDFILEDAASPKCIMKEKKKPGE TFFMCSCSSDECNDNIIFSEEYNTS NPD	
117	DKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSP GIPPHVQKSVNNDMIVTDNNGAVKF PQLCKFCDVRFSTCDNQKSCMSNCS ITSICEKPQEVCVAVWRKNDENITL ETVCHDPKLPYHDFILEDAASPKCI MKEKKKPGETFFMCSCSSDECNDNI IFSEEYNTSNPDIPPHVQKSDVEME AQKDEIIAPSANRTAHPLRHINNDM IVTDNNGAVKFPQLCKFCDVRFSTC DNQKSCMSNCSITSICEKPQEVCVA VWRKNDENITLETVCHDPKLPYHDF ILEDAASPKCIMKEKKKPGETFFMC SCSSDECNDNIIFSEEYNTSNPDIP PHVQKSDVEMEAQKDEIIAPSANRT AHPLRHINNDMIVTDNNGAVKFPQL CKFCDVRFSTCDNQKSCMSNCSITS ICEKPQEVCVAVWRKNDENITLETV CHDPKLPYHDFILEDAASPKCIMKE KKKPGETFFMCSCSSDECNDNIIFS EEYNTSNPD	hIgG1FcΔK-CC-T2-T2b^{AA}-T2b^{AA} fusion
118	VECPPCPAPPVAGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVQ FNWYVDGVEVHNAKTKPREEQFNST FRVVSVLTVVHQDWLNGKEYKCKVS NKGLPAPIEKTISKTKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYP SDISVEWESNGQPENNYKTTPPMLD SDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGIPP HVQKSVNNDMIVTDNNGAVKFPQLC KFCDVRFSTCDNQKSCMSNCSITSI CEKPQEVCVAVWRKNDENITLETVC HDPKLPYHDFILEDAASPKCIMKEK KKPGETFFMCSCSSDECNDNIIFSE EYNTSNPDIPPHVQKSDVEMEAQKD EIIAPSANRTAHPLRHINNDMIVTD NNGAVKFPQLCKFCDVRFSTCDNQK SCMSNCSITSICEKPQEVCVAVWRK NDENITLETVCHDPKLPYHDFILED AASPKCIMKEKKKPGETFFMCSCSS DECNDNIIFSEEYNTSNPDIPPHVQ KSDVEMEAQKDEIIAPSANRTAHPL RHINNDMIVTDNNGAVKFPQLCKFC DVRFSTCDNQKSCMSNCSITSICEK PQEVCVAVWRKNDENITLETVCHDP KLPYHDFILEDAASPKCIMKEKKKP GETFFMCSCSSDECNDNIIFSEEYN TSNPD	hIgG2FcΔK-CC-T2-T2b^{AA}-T2b^{AA} fusion
119	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLGIPPHVQKSVNNDMIVTDNNGAV KFPQLCKFCDVRFSTCDNQKSCMSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPDIPPHVQKSDVE MEAQKDEIIAPSANRTAHPLRHINN DMIVTDNNGAVKFPQLCKFCDVRFS TCDNQKSCMSNCSITSICEKPQEVC VAVWRKNDENITLETVCHDPKLPYH DFILEDAASPKCIMKEKKKPGETFF MCSCSSDECNDNIIFSEEYNTSNPD IPPHVQKSDVEMEAQKDEIIAPSAN RTAHPLRHINNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPD	hIgG4FcΔK-CC-228P-T2-T2b^{AA}-T2b^{AA} fusion
120	ESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSKLTVDKSRWQ EGNVFSCSVMHEALHNHYTQKSLSL SLGIPPHVQKSVNNDMIVTDNNGAV KFPQLCKFCDVRFSTCDNQKSCMSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPDIPPHVQKSDVE MEAQKDEIIAPSANRTAHPLRHINN DMIVTDNNGAVKFPQLCKFCDVRFS TCDNQKSCMSNCSITSICEKPQEVC VAVWRKNDENITLETVCHDPKLPYH DFILEDAASPKCIMKEKKKPGETFF MCSCSSDECNDNIIFSEEYNTSNPD IPPHVQKSDVEMEAQKDEIIAPSAN RTAHPLRHINNDMIVTDNNGAVKFP QLCKFCDVRFSTCDNQKSCMSNCSI TSICEKPQEVCVAVWRKNDENITLE TVCHDPKLPYHDFILEDAASPKCIM KEKKKPGETFFMCSCSSDECNDNII FSEEYNTSNPD	hIgG4FcΔK-CC-228P-409K-T2-T2b^{AA}-T2b^{AA} fusion
121	DILLTQSPVILSVSPGERVSFSCRA SQSIGTNIHWYQQRTNGSPRLLIKY ASESISGIPSRFSGSGSGTDFTLSI NSVESEDIADYYCQQNNNWPTTFGA GTKLELKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	Cetuximab LC
122	QVQLKQSGPGLVQPSQSLSITCTVS GFSLTNYGVHWVRQSPGKGLEWLGV IWSGGNTDYNTPFTSRLSINKDNSK SQVFFKMNSLQSNDTAIYYCARALT YYDYEFAYWGQGTLVTVSAASTKGP	Cetuximab HC-T22d35

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SEQ ID NO:	Sequence	Description
	SVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKRVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGKI PPHVQKSVNNDMIVTDNNGAVKFPQ LCKFCDVRFSTCDNQKSCMSNCSIT SICEKPQEVCVAVWRKNDENITLET VCHDPKLPYHDFILEDAASPKCIMK EKKKPGETFFMCSCSSDECNDNIIF SEEYNTSNPDIPPHVQKSVNNDMIV TDNNGAVKFPQLCKFCDVRFSTCDN QKSCMSNCSITSICEKPQEVCVAVW RKNDENITLETVCHDPKLPYHDFIL EDAASPKCIMKEKKKPGETFFMCSC SSDECNDNIIFSEEYNTSNPD	
123	QVQLKQSGPGLVQPSQSLSITCTVS GFSLTNYGVHWVRQSPGKGLEWLGV IWSGGNTDYNTPFTSRLSINKDNSK SQVFFKMNSLQSNDTAIYYCARALT YYDYEFAYWGQGTLVTVSAASTKGP SVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKRVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGKI PPHVQKSVNNDMIVTDNNGAVKFPQ LCKFCDVRFSTCDNQKSCMSNCSIT SICEKPQEVCVAVWRKNDENITLET VCHDPKLPYHDFILEDAASPKCIMK EKKKPGETFFMCSCSSDECNDNIIF SEEYNTSNPD	Cetuximab HC-T2m
124	DIQMTQSPSSLSASVGDRVTITCRA SQDVNTAVAWYQQKPGKAPKLLIYS ASFLYSGVPSRFSGSRSGTDFTLTI SSLQPEDFATYYCQQHYTTPPTFGQ GTKVEIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	Herceptin LC
125	EVQLVESGGGLVQPGGSLRLSCAAS GFNIKDTYIHWVRQAPGKGLEWVAR IYPTNGYTRYADSVKGRFTISADTS KNTAYLQMNSLRAEDTAVYYCSRWGG DGFYAMDYWGQGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVS	Herceptin HC-T22d35

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SEQ ID NO:	Sequence	Description
	NKALPAPIEKTISKAKGQPREPQVY TLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGKIP PHVQKSVNNDMIVTDNNGAVKFPQL CKFCDVRFSTCDNQKSCMSNCSITS ICEKPQEVCVAVWRKNDENITLETV CHDPKLPYHDFILEDAASPKCIMKE KKKPGETFFMCSCSSDECNDNIIFS EEYNTSNPDIPPHVQKSVNNDMIVT DNNGAVKFPQLCKFCDVRFSTCDNQ KSCMSNCSITSICEKPQEVCVAVWR KNDENITLETVCHDPKLPYHDFILE DAASPKCIMKEKKKPGETFFMCSCS SDECNDNIIFSEEYNTSNPD	
126	DIQMTQSPSSLSASVGDRVTITCSA SQDISNYLNWYQQKPGKAPKVLIYF TSSLHSGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQYSTVPWTFGQ GTKVEIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	Avastin LC
127	EVQLVESGGGLVQPGGSLRLSCAAS GYTFTNYGMNWVRQAPGKGLEWVGW INTYTGEPTYAADFKRRFTFSLDTS KSTAYLQMNSLRAEDTAVYYCAKYP HYYGSSHWYFDVWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLS PGKIPPHVQKSVNNDMIVTDNNGAV KFPQLCKFCDVRFSTCDNQKSCMSN CSITSICEKPQEVCVAVWRKNDENI TLETVCHDPKLPYHDFILEDAASPK CIMKEKKKPGETFFMCSCSSDECND NIIFSEEYNTSNPDIPPHVQKSVNN DMIVTDNNGAVKFPQLCKFCDVRFS TCDNQKSCMSNCSITSICEKPQEVC VAVWRKNDENITLETVCHDPKLPYH DFILEDAASPKCIMKEKKKPGETFF MCSCSSDECNDNIIFSEEYNTSNPD	Avastin HC-T22d35
128	DIQMTQSPSTLSASVGDRVTITCKC QLSVGYMHWYQQKPGKAPKLLIYDT SKLASGVPSRFSGSGSGTEFTLTIS SLQPDDFATYYCFQGSGYPFTFGGG TKLEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC	Synagis LC
129	QVTLRESGPALVKPTQTLTLTCTFS GFSLSTSGMSVGWIRQPPGKALEWL ADIWWDDKKDYNPSLKSRLTISKDT SKNQVVLKVTNMDPADTATYYCARS MITNWYFDVWGAGTTVTVSSASTKG PSVFPLAPSSAAAAGGTAALGCLVK	Synagis HC-T22d35

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SEQ ID NO:	Sequence	Description
	DYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKRVEPKSCDK THTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGI PPHVQKSVNNDMIVTDNNGAVKFPQ LCKFCDVRFSTCDNQKSCMSNCSIT SICEKPQEVCVAVWRKNDENITLET VCHDPKLPYHDFILEDAASPKCIMK EKKKPGETFFMCSCSSDECNDNIIF SEEYNTSNPDIPPHVQKSVNNDMIV TDNNGAVKFPQLCKFCDVRFSTCDN QKSCMSNCSITSICEKPQEVCVAVW RKNDENITLETVCHDPKLPYHDFIL EDAASPKCIMKEKKKPGETFFMCSC SSDECNDNIIFSEEYNTSNPD	
130	EVQLQASGGGLVQAGGSLRLSCAAS GFKITHYTMGWFRQAPGKEREFVSR ITWGGDNTFYSNSVKGRFTISRDNA KNTVYLQMNSLKPEDTADYYCAAGST STATPLRVDYWGKGTQVTVSSASEPR GPTIKPCPPCKCPAPNLLGGPSVFI FPPKIKDVLMISLSPIVTCVVVDVS EDDPDVQISWFVNNVEVHTAQTQTH REDYNSTLRVVSALPIQHQDWMSGK EFKCKVNNKDLPAPIERTISKPKGS VRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYK NTEPVLDSDCSYFMYSKLRVEKKNW VERNSYSCSVVHEGLHNHHTTKSFS RTPGTGIPPHVQKSVNNDMIVTDNN CAVKFPQLCKFCDVRFSTCDNQKSC MSNCSITSICEKPQEVCVAVWRKND ENITLETVCHDPKLPYHDFILEDAA SPKCIMKEKKKPGETFFMCSCSSDE CNDNIIFSEEYNTSNPDIPPHVQKS VNNDMIVTDNNGAVKFPQLCKFCDV RFSTCDNQKSCMSNCSITSICEKPQ EVCVAVWRKNDENITLETVCHDPKL PYHDFILEDAASPKCIMKEKKKPGE TFFMCSCSSDECNDNIIFSEEYNTS NPD	FC5-Fc-T22d35
131	EVQLQASGGGLVQAGGSLRLSCAAS GFKITHYTMGWFRQAPGKEREFVSR ITWGGDNTFYSNSVKGRFTISRDNA KNTVYLQMNSLKPEDTADYYCAAGS TSTATPLRVDYWGKCTQVTVSSASE PRGPTIKPCPPCKCPAPNLLGGPSV FIFPPKIKDVLMISLSPIVTCVVVD VSEDDPDVQISWFVNNVEVHTAQTQ THREDYNSTLRVVSALPIQHQDWMS GKEFKCKVNNKDLPAPIERTISKPK GSVRAPQVYVLPPPEEEMTKKQVTL TCMVTDFMPEDIYVEWTNNGKTELN YKNTEPVLDSDGSYFMYSKLRVEKK NWVERNSYSCSVVHEGLHNHHTTKS FSRTPGTGIPPHVQKSVNNDMIVTD NNGAVKFPQLCKFCDVRFSTCDNQK SCMSNCSITSICEKPQEVCVAVWRK NDENITLETVCHDPKLPYHDFILED AASPKCIMKEKKKPGETFFMCSCSS DECNDNIIFSEEYNTSNPD	FC5-Fc-T2m

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SEQ ID NO:	Sequence	Description
132	MGRGLLRGLWPLHIVLWTRIASTIP PHVQKSVNNDMIVTDNNGAVKFPQL CKFCDVRFSTCDNQKSCMSNCSITS ICEKPQEVCVAVWRKNDENITLETV CHDPKLPYHDFILEDAASPKCIMKE KKKPCETFFMCSCSSDECNDNIIFS EEYNTSNPDMDPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK	T2-hIgG1Fc fusion from R&D, also termed T2m-Fc (R&D)
133	MDWTWRILFLVAAATGTHAIPPHVQ KSVNNDMIVTDNNGAVKFPQLCKFC DVRFSTCDNQKSCMSNCSITSICEK PQEVCVAVWRKNDENITLETVCHDP KLPYHDFILEDAASPKCIMKEKKKP GETFFMCSCSSDECNDNIIFSEEYN TSNPDERKCCVECPPCPAPPVACPS VFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDISVEWESNGQPEN NYKTTPPMLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPG	T2-hIgG2Fc-CCCC fusion, also termed T2m-Fc
134	LPYHDFILEDAASPK	Isotope-labelled peptide for T22d35
135	ALPAPIEK	Isotope-labelled peptide for Cetuximab
136	DDDDDDDDDDDDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGIPPHVQKSVNNDMI VTDNNGAVKFPQLCKFCDVRFSTCD NQKSCMSNCSITSICEKPQEVCVAV WRKNDENITLETVCHDPKLPYHDFI LEDAASPKCIMKEKKKPGETFFMCS CSSDECNDNIIFSEEYNTSNPD	D10-hIgG1FcΔK-CC-T2m fusion
137	DDDDDDDDDDGGGSDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGIPPHVQKSVN NDMIVTDNNGAVKFPQLCKFCDVRF STCDNQKSCMSNCSITSICEKPQEV CVAVWRKNDENITLETVCHDPKLPY	D10-GsS-hIgG1FcΔK-CC-T2m fusion

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SEQ ID NO:	Sequence	Description
	HDFILEDAASPKCIMKEKKKPGETF FMCSCSSDECNDNIIFSEEYNTSNP D	
138	DDDDDDDDDDPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSL SLSPGIPPHVQKSVNNDMIVTDNNG AVKFPQLCKFCDVRFSTCDNQKSCM SNCSITSICEKPQEVCVAVWRKNDE NITLETVCHDPKLPYHDFILEDAAS PKCIMKEKKKPGETFFMCSCSSDEC NDNIIFSEEYNTSNPD	D10-hIgG1FcΔK-C-T2m fusion
139	DDDDDDDDDDGGGSGGGSPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGIPPHVQKSVNND MIVTDNNGAVKFPQLCKFCDVRFST CDNQKSCMSNCSITSICEKPQEVCV AVWRKNDENITLETVCHDPKLPYHD FILEDAASPKCIMKEKKKPGETFFM CSCSSDECNDNIIFSEEYNTSNPD	D10-$(G_3S)_2$-hIgG1FcΔK-C-T2m fusion
140	DDDDDDDDDDVECPPCPAPPVAGPS VFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKT KGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDISVEWESNGQPEN NYKTTPPMLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGIPPHVQKSVNNDMIVTDN NGAVKFPQLCKFCDVRFSTCDNQKS CMSNCSITSICEKPQEVCVAVWRKN DENITLETVCHDPKLPYHDFILEDA ASPKCIMKEKKKPGETFFMCSCSSD ECNDNIIFSEEYNTSNPD	D10-hIgG2FcΔK-CC-T2m fusion
141	DDDDDDDDDDDESKYGPPCPPCPAPE FLCCPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGIPPHVQKSVNND MIVTDNNGAVKFPQLCKFCDVRFST CDNQKSCMSNCSITSICEKPQEVCV AVWRKNDENITLETVCHDPKLPYHD FILEDAASPKCIMKEKKKPGETFFM CSCSSDECNDNIIFSEEYNTSNPD	D10-hIgG4FcΔK-CC-228P-T2m fusion
142	DDDDDDDDDDDESKYGPPCPPCPAPE FLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNCKEYKCKVSNKGLPSSIE	D10-hIgG4FcΔK-CC-228P-409K-T2m fusion

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SEQ ID NO:	Sequence	Description
	KTISKAKGQPREPQVYTLPPSQEEM TKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGIPPHVQKSVNND MIVTDNNGAVKFPQLCKFCDVRFST CDNQKSCMSNCSITSICEKPQEVCV AVWRKNDENITLETVCHDPKLPYHD FILEDAASPKCIMKEKKKPGETFFM CSCSSDECNDNIIFSEEYNTSNPD	
143	DDDDDDDDDDDDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLH QDWLNCKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGIPPHVQKSVNNDMI VTDNNGAVKFPQLCKFCDVRFSTCD NQKSCMSNCSITSICEKPQEVCVAV WRKNDENITLETVCHDPKLPYHDFI LEDAASPKCIMKEKKKPGETFFMCS CSSDECNDNIIFSEEYNTSNPDIPP HVQKSVNNDMIVTDNNGAVKFPQLC KFCDVRFSTCDNQKSCMSNCSITSI CEKPQEVCVAVWRKNDENITLETVC HDPKLPYHDFILEDAASPKCIMKEK KKPGETFFMCSCSSDECNDNIIFSE EYNTSNPD	D10-hIgG1FcΔK-CC-T22d35 fusion
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U.S. 62/777,375

US2015/0225483

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            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

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

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

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

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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Lys Ser Leu Ser Leu Ser Pro Gly Lys
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Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
        35                  40                  45

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    50                  55                  60

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
65                  70                  75                  80

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
                85                  90                  95

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
            100                 105                 110

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        115                 120                 125

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    130                 135                 140

Asp Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145                 150                 155                 160
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Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                165                 170                 175

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
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Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
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Ser Leu Ser Leu Ser Pro Gly Lys
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Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

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

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile
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Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln
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Lys Ser Leu Ser Leu Ser Pro Gly Lys
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            20                  25                  30

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
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Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

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

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
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Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Leu Gly Lys
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Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
            20                  25                  30
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Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
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Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

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

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

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

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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35 40 45

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
50 55 60

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
65 70 75 80

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
85 90 95

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
100 105 110

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

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
130 135 140

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
145 150 155 160

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
165 170 175

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
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Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-CC Fc variant

<400> SEQUENCE: 11

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

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Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

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

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

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly
225


<210> SEQ ID NO 12
<211> LENGTH: 231
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-S Fc variant

<400> SEQUENCE: 12

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                   10                  15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50                  55                  60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly
225                 230


<210> SEQ ID NO 13
<211> LENGTH: 231
```

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1deltaK-SS Fc variant

<400> SEQUENCE: 13

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro Gly
225 230

<210> SEQ ID NO 14
<211> LENGTH: 231
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-SSS Fc variant

<400> SEQUENCE: 14

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro Pro Ser Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

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Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly
225                 230


<210> SEQ ID NO 15
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-deltaC Fc variant

<400> SEQUENCE: 15

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1               5                   10                  15

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            20                  25                  30

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
        35                  40                  45

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    50                  55                  60

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
65                  70                  75                  80

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
                85                  90                  95

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
            100                 105                 110

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        115                 120                 125

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    130                 135                 140

Asp Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145                 150                 155                 160

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                165                 170                 175

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

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        195                 200                 205

Ser Leu Ser Leu Ser Pro Gly
    210                 215
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<210> SEQ ID NO 16
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-C Fc variant

<400> SEQUENCE: 16

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
1 5 10 15

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
20 25 30

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
35 40 45

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
50 55 60

Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr
65 70 75 80

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
85 90 95

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
100 105 110

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
115 120 125

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
130 135 140

Phe Tyr Pro Ser Asp Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro
145 150 155 160

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
165 170 175

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
180 185 190

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
195 200 205

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> SEQ ID NO 17
<211> LENGTH: 222
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-CC Fc variant

<400> SEQUENCE: 17

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
1 5 10 15

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
20 25 30

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
35 40 45

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
50 55 60

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
65 70 75 80

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

```
                85                  90                  95

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            100                 105                 110

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
        115                 120                 125

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    130                 135                 140

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

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                165                 170                 175

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            180                 185                 190

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        195                 200                 205

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215                 220


<210> SEQ ID NO 18
<211> LENGTH: 228
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2Fc-CCCC Fc variant

<400> SEQUENCE: 18

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
1               5                   10                  15

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            20                  25                  30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        35                  40                  45

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
    50                  55                  60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
65                  70                  75                  80

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
                85                  90                  95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
            100                 105                 110

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
        115                 120                 125

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
    130                 135                 140

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

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

Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            180                 185                 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        195                 200                 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    210                 215                 220

Ser Pro Gly Lys
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225

<210> SEQ ID NO 19
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-SS Fc variant

<400> SEQUENCE: 19

Glu Arg Lys Ser Ser Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
1 5 10 15

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
65 70 75 80

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
100 105 110

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
130 135 140

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

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

Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
210 215 220

Ser Pro Gly
225

<210> SEQ ID NO 20
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-SSS Fc variant

<400> SEQUENCE: 20

Glu Arg Lys Ser Ser Val Glu Ser Pro Pro Cys Pro Ala Pro Pro Val
1 5 10 15

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

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Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
65                  70                  75                  80

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
                85                  90                  95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
            100                 105                 110

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
        115                 120                 125

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
    130                 135                 140

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

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

Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            180                 185                 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        195                 200                 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    210                 215                 220

Ser Pro Gly
225


<210> SEQ ID NO 21
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-SSSS Fc variant

<400> SEQUENCE: 21

Glu Arg Lys Ser Ser Val Glu Ser Pro Pro Ser Pro Ala Pro Pro Val
1               5                   10                  15

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            20                  25                  30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        35                  40                  45

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
    50                  55                  60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
65                  70                  75                  80

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
                85                  90                  95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
            100                 105                 110

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
        115                 120                 125

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
    130                 135                 140

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

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

Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            180                 185                 190
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Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        195                 200                 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    210                 215                 220

Ser Pro Gly
225


<210> SEQ ID NO 22
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG3FcdeltaK-deltaC Fc variant

<400> SEQUENCE: 22

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

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

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

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215


<210> SEQ ID NO 23
<211> LENGTH: 220
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG3FcdeltaK-C Fc variant

<400> SEQUENCE: 23

Pro Arg Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
1               5                   10                  15

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            20                  25                  30

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
        35                  40                  45
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Phe Lys Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    50                  55                  60

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu
65                  70                  75                  80

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                85                  90                  95

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            100                 105                 110

Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
        115                 120                 125

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    130                 135                 140

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln
145                 150                 155                 160

Pro Glu Asn Asn Tyr Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
                165                 170                 175

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            180                 185                 190

Gln Gly Asn Ile Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        195                 200                 205

Arg Phe Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    210                 215                 220


<210> SEQ ID NO 24
<211> LENGTH: 226
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG3FcdeltaK-CC Fc variant

<400> SEQUENCE: 24

Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Phe
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

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

Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn Tyr Asn Thr Thr Pro Pro
                165                 170                 175

Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190
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```
Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn Arg Phe Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly
225


<210> SEQ ID NO 25
<211> LENGTH: 231
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG3FcdeltaK-S Fc variant

<400> SEQUENCE: 25

Glu Pro Lys Ser Ser Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro Ala
1               5                   10                  15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr Val
    50                  55                  60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80

Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly
225                 230


<210> SEQ ID NO 26
<211> LENGTH: 231
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG3FcdeltaK-SS Fc variant

<400> SEQUENCE: 26

Glu Pro Lys Ser Ser Asp Thr Pro Pro Pro Ser Pro Arg Cys Pro Ala
1               5                   10                  15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
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            20                  25                  30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr Val
    50                  55                  60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80

Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly
225                 230


<210> SEQ ID NO 27
<211> LENGTH: 231
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG3FcdeltaK-SSS Fc variant

<400> SEQUENCE: 27

Glu Pro Lys Ser Ser Asp Thr Pro Pro Pro Ser Pro Arg Ser Pro Ala
1               5                   10                  15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr Val
    50                  55                  60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80

Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
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145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly
225                 230


<210> SEQ ID NO 28
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-deltaC Fc variant

<400> SEQUENCE: 28

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

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

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

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Leu Gly
    210                 215


<210> SEQ ID NO 29
<211> LENGTH: 220
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-C Fc variant

<400> SEQUENCE: 29
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Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu
1               5                   10                  15

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            20                  25                  30

Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
        35                  40                  45

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    50                  55                  60

Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu
65                  70                  75                  80

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                85                  90                  95

Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
            100                 105                 110

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

Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    130                 135                 140

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
145                 150                 155                 160

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                165                 170                 175

Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
            180                 185                 190

Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        195                 200                 205

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
    210                 215                 220


<210> SEQ ID NO 30
<211> LENGTH: 228
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC Fc variant

<400> SEQUENCE: 30

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140
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Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145                 150                 155                 160

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly
225


<210> SEQ ID NO 31
<211> LENGTH: 228
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P Fc variant

<400> SEQUENCE: 31

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly
225


<210> SEQ ID NO 32
<211> LENGTH: 228
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P-409K Fc variant

<400> SEQUENCE: 32

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
180 185 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
195 200 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
210 215 220

Leu Ser Leu Gly
225

<210> SEQ ID NO 33
<211> LENGTH: 228
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-S Fc variant

<400> SEQUENCE: 33

Glu Ser Lys Tyr Gly Pro Pro Ser Pro Ser Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

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Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly
225


<210> SEQ ID NO 34
<211> LENGTH: 228
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-SS Fc variant

<400> SEQUENCE: 34

Glu Ser Lys Tyr Gly Pro Pro Ser Pro Ser Ser Pro Ala Pro Glu Phe
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly
225
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<210> SEQ ID NO 35
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRII-ED structured domain

<400> SEQUENCE: 35

Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
1 5 10 15

Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
20 25 30

Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
35 40 45

Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
50 55 60

Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
65 70 75 80

Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
85 90 95

Asp Asn Ile Ile Phe
100

<210> SEQ ID NO 36
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRII-ED N-term unstructured region and natural linker

<400> SEQUENCE: 36

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
1 5 10 15

Asp Asn Asn Gly Ala Val Lys Phe Pro
20 25

<210> SEQ ID NO 37
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRIIb-ED N-term unstructured region and natural linker

<400> SEQUENCE: 37

Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys
1 5 10 15

Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro Leu Arg
20 25 30

His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys
35 40 45

Phe Pro
50

<210> SEQ ID NO 38
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRIIb-ED Cys-mutated N-term unstructured

region and natural linker

<400> SEQUENCE: 38

Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys
1 5 10 15

Asp Glu Ile Ile Ala Pro Ser Ala Asn Arg Thr Ala His Pro Leu Arg
20 25 30

His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys
35 40 45

Phe Pro
50

<210> SEQ ID NO 39
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRII-ED C-term unstructured region and natural linker

<400> SEQUENCE: 39

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
1 5 10

<210> SEQ ID NO 40
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRII-ED natural linker

<400> SEQUENCE: 40

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln
1 5 10 15

Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val
20 25 30

Lys Phe Pro
35

<210> SEQ ID NO 41
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRIIb-ED natural linker

<400> SEQUENCE: 41

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln
1 5 10 15

Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro
20 25 30

Ser Cys Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met
35 40 45

Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
50 55 60

<210> SEQ ID NO 42
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRIIb-ED Cys-mutated linker

<400> SEQUENCE: 42

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln
1 5 10 15

Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro
20 25 30

Ser Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met
35 40 45

Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
50 55 60

<210> SEQ ID NO 43
<211> LENGTH: 136
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRII-ED monomer, also termed T2 or T2m

<400> SEQUENCE: 43

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
1 5 10 15

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
20 25 30

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
35 40 45

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
50 55 60

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
65 70 75 80

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
85 90 95

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
100 105 110

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
115 120 125

Glu Tyr Asn Thr Ser Asn Pro Asp
130 135

<210> SEQ ID NO 44
<211> LENGTH: 161
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetabRIIb-ED monomer, also termed T2b

<400> SEQUENCE: 44

Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys
1 5 10 15

Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro Leu Arg
20 25 30

His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys
35 40 45

Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp
50 55 60

Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu
65 70 75 80

Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn
85 90 95

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Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp
            100                 105                 110

Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys
        115                 120                 125

Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu
    130                 135                 140

Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro
145                 150                 155                 160

Asp


<210> SEQ ID NO 45
<211> LENGTH: 161
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRIIb-ED monomer Cys-mutated in the linker
      region, also termed T2bAA

<400> SEQUENCE: 45

Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys
1               5                   10                  15

Asp Glu Ile Ile Ala Pro Ser Ala Asn Arg Thr Ala His Pro Leu Arg
            20                  25                  30

His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys
        35                  40                  45

Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp
    50                  55                  60

Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu
65                  70                  75                  80

Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn
                85                  90                  95

Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp
            100                 105                 110

Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys
        115                 120                 125

Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu
    130                 135                 140

Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro
145                 150                 155                 160

Asp


<210> SEQ ID NO 46
<211> LENGTH: 272
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRII-ED dimer, also termed T2-T2 or T22d35

<400> SEQUENCE: 46

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
1               5                   10                  15

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
            20                  25                  30

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
        35                  40                  45

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
    50                  55                  60
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Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
65                  70                  75                  80

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
                85                  90                  95

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
            100                 105                 110

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
        115                 120                 125

Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser
    130                 135                 140

Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe
145                 150                 155                 160

Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn
                165                 170                 175

Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys
            180                 185                 190

Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile
        195                 200                 205

Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe
    210                 215                 220

Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys
225                 230                 235                 240

Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys
                245                 250                 255

Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            260                 265                 270


<210> SEQ ID NO 47
<211> LENGTH: 322
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRIIb-ED dimer, also termed T2-T2b

<400> SEQUENCE: 47

Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys
1               5                   10                  15

Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro Leu Arg
            20                  25                  30

His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys
        35                  40                  45

Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp
    50                  55                  60

Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu
65                  70                  75                  80

Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn
                85                  90                  95

Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp
            100                 105                 110

Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys
        115                 120                 125

Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu
    130                 135                 140

Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro
145                 150                 155                 160
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Asp Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln
                165                 170                 175

Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro Leu
            180                 185                 190

Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val
        195                 200                 205

Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys
    210                 215                 220

Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys
225                 230                 235                 240

Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu
                245                 250                 255

Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His
            260                 265                 270

Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu
        275                 280                 285

Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp
    290                 295                 300

Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn
305                 310                 315                 320

Pro Asp


<210> SEQ ID NO 48
<211> LENGTH: 322
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRIIb-ED dimer Cys-mutated in the linker
      region, also termed T2-T2bAA

<400> SEQUENCE: 48

Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys
1               5                   10                  15

Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro Leu Arg
            20                  25                  30

His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys
        35                  40                  45

Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp
    50                  55                  60

Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu
65                  70                  75                  80

Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn
                85                  90                  95

Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp
            100                 105                 110

Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys
        115                 120                 125

Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu
    130                 135                 140

Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro
145                 150                 155                 160

Asp Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln
                165                 170                 175

Lys Asp Glu Ile Ile Ala Pro Ser Ala Asn Arg Thr Ala His Pro Leu
            180                 185                 190
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Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val
        195                 200                 205

Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys
    210                 215                 220

Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys
225                 230                 235                 240

Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu
                245                 250                 255

Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His
            260                 265                 270

Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu
        275                 280                 285

Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp
    290                 295                 300

Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn
305                 310                 315                 320

Pro Asp


<210> SEQ ID NO 49
<211> LENGTH: 408
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRII-ED trimer, also termed T2-T2-T2

<400> SEQUENCE: 49

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
1               5                   10                  15

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
            20                  25                  30

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
        35                  40                  45

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
    50                  55                  60

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
65                  70                  75                  80

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
                85                  90                  95

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
            100                 105                 110

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
        115                 120                 125

Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser
    130                 135                 140

Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe
145                 150                 155                 160

Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn
                165                 170                 175

Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys
            180                 185                 190

Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile
        195                 200                 205

Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe
    210                 215                 220

Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys
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225                 230                 235                 240

Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys
                245                 250                 255

Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            260                 265                 270

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
        275                 280                 285

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
    290                 295                 300

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
305                 310                 315                 320

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
                325                 330                 335

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
            340                 345                 350

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
        355                 360                 365

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
    370                 375                 380

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
385                 390                 395                 400

Glu Tyr Asn Thr Ser Asn Pro Asp
                405


<210> SEQ ID NO 50
<211> LENGTH: 458
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRIIb-ED trimer, also termed T2-T2b-T2b

<400> SEQUENCE: 50

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
1               5                   10                  15

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
            20                  25                  30

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
        35                  40                  45

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
    50                  55                  60

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
65                  70                  75                  80

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
                85                  90                  95

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
            100                 105                 110

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
        115                 120                 125

Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser
    130                 135                 140

Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys
145                 150                 155                 160

Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val
                165                 170                 175

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
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            180                 185                 190

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
        195                 200                 205

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
    210                 215                 220

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
225                 230                 235                 240

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
                245                 250                 255

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
            260                 265                 270

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
        275                 280                 285

Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys
    290                 295                 300

Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser
305                 310                 315                 320

Cys Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile
                325                 330                 335

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
            340                 345                 350

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
        355                 360                 365

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
    370                 375                 380

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
385                 390                 395                 400

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
                405                 410                 415

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
            420                 425                 430

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
        435                 440                 445

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
    450                 455


<210> SEQ ID NO 51
<211> LENGTH: 458
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRIIb-ED trimer Cys-mutated in the linker
      regions, also termed T2-T2bAA-T2bAA

<400> SEQUENCE: 51

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
1               5                   10                  15

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
            20                  25                  30

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
        35                  40                  45

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
    50                  55                  60

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
65                  70                  75                  80
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Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
                85                  90                  95

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
            100                 105                 110

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
        115                 120                 125

Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser
    130                 135                 140

Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro Ser Ala
145                 150                 155                 160

Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val
                165                 170                 175

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
            180                 185                 190

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
        195                 200                 205

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
    210                 215                 220

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
225                 230                 235                 240

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
                245                 250                 255

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
            260                 265                 270

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
        275                 280                 285

Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys
    290                 295                 300

Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro Ser
305                 310                 315                 320

Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile
                325                 330                 335

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
            340                 345                 350

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
        355                 360                 365

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
    370                 375                 380

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
385                 390                 395                 400

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
                405                 410                 415

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
            420                 425                 430

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
        435                 440                 445

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
    450                 455
```

<210> SEQ ID NO 52
<211> LENGTH: 79
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-ED structured domain

<400> SEQUENCE: 52

Ala Leu Gln Cys Phe Cys His Leu Cys Thr Lys Asp Asn Phe Thr Cys
1 5 10 15

Val Thr Asp Gly Leu Cys Phe Val Ser Val Thr Glu Thr Thr Asp Lys
20 25 30

Val Ile His Asn Ser Met Cys Ile Ala Glu Ile Asp Leu Ile Pro Arg
35 40 45

Asp Arg Pro Phe Val Cys Ala Pro Ser Ser Lys Thr Gly Ser Val Thr
50 55 60

Thr Thr Tyr Cys Cys Asn Gln Asp His Cys Asn Lys Ile Glu Leu
65 70 75

<210> SEQ ID NO 53
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-ED N-term unstructured region and natural linker

<400> SEQUENCE: 53

Ala Ala Leu Leu Pro Gly Ala Thr
1 5

<210> SEQ ID NO 54
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-ED C-term unstructured region and natural linker

<400> SEQUENCE: 54

Pro Thr Thr Val Lys Ser Ser Pro Gly Leu Gly Pro Val Glu
1 5 10

<210> SEQ ID NO 55
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-ED natural linker

<400> SEQUENCE: 55

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

Leu Leu Pro Gly Ala Thr
20

<210> SEQ ID NO 56
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-ED monomer, also termed T1 or T1m

<400> SEQUENCE: 56

Ala Ala Leu Leu Pro Gly Ala Thr Ala Leu Gln Cys Phe Cys His Leu
1 5 10 15

Cys Thr Lys Asp Asn Phe Thr Cys Val Thr Asp Gly Leu Cys Phe Val
20 25 30

Ser Val Thr Glu Thr Thr Asp Lys Val Ile His Asn Ser Met Cys Ile

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        35                  40                  45

Ala Glu Ile Asp Leu Ile Pro Arg Asp Arg Pro Phe Val Cys Ala Pro
    50                  55                  60

Ser Ser Lys Thr Gly Ser Val Thr Thr Thr Tyr Cys Cys Asn Gln Asp
65                  70                  75                  80

His Cys Asn Lys Ile Glu Leu Pro Thr Thr Val Lys Ser Ser Pro Gly
                85                  90                  95

Leu Gly Pro Val Glu
            100


<210> SEQ ID NO 57
<211> LENGTH: 202
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-ED dimer, also termed T1-T1

<400> SEQUENCE: 57

Ala Ala Leu Leu Pro Gly Ala Thr Ala Leu Gln Cys Phe Cys His Leu
1               5                   10                  15

Cys Thr Lys Asp Asn Phe Thr Cys Val Thr Asp Gly Leu Cys Phe Val
            20                  25                  30

Ser Val Thr Glu Thr Thr Asp Lys Val Ile His Asn Ser Met Cys Ile
        35                  40                  45

Ala Glu Ile Asp Leu Ile Pro Arg Asp Arg Pro Phe Val Cys Ala Pro
    50                  55                  60

Ser Ser Lys Thr Gly Ser Val Thr Thr Thr Tyr Cys Cys Asn Gln Asp
65                  70                  75                  80

His Cys Asn Lys Ile Glu Leu Pro Thr Thr Val Lys Ser Ser Pro Gly
                85                  90                  95

Leu Gly Pro Val Glu Ala Ala Leu Leu Pro Gly Ala Thr Ala Leu Gln
            100                 105                 110

Cys Phe Cys His Leu Cys Thr Lys Asp Asn Phe Thr Cys Val Thr Asp
        115                 120                 125

Gly Leu Cys Phe Val Ser Val Thr Glu Thr Thr Asp Lys Val Ile His
    130                 135                 140

Asn Ser Met Cys Ile Ala Glu Ile Asp Leu Ile Pro Arg Asp Arg Pro
145                 150                 155                 160

Phe Val Cys Ala Pro Ser Ser Lys Thr Gly Ser Val Thr Thr Thr Tyr
                165                 170                 175

Cys Cys Asn Gln Asp His Cys Asn Lys Ile Glu Leu Pro Thr Thr Val
            180                 185                 190

Lys Ser Ser Pro Gly Leu Gly Pro Val Glu
        195                 200


<210> SEQ ID NO 58
<211> LENGTH: 39
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-TbetaRII-ED natural linker

<400> SEQUENCE: 58

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

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
            20                  25                  30
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Asn Gly Ala Val Lys Phe Pro
        35


<210> SEQ ID NO 59
<211> LENGTH: 64
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-TbetaRIIb-ED natural linker

<400> SEQUENCE: 59

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

Pro His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu
            20                  25                  30

Ile Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro Leu Arg His Ile
        35                  40                  45

Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
    50                  55                  60


<210> SEQ ID NO 60
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRII-TbetaRI-ED natural linker

<400> SEQUENCE: 60

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ala Ala Leu Leu Pro Gly
1               5                   10                  15

Ala Thr


<210> SEQ ID NO 61
<211> LENGTH: 237
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-TbetaRII-ED dimer T1-T2

<400> SEQUENCE: 61

Ala Ala Leu Leu Pro Gly Ala Thr Ala Leu Gln Cys Phe Cys His Leu
1               5                   10                  15

Cys Thr Lys Asp Asn Phe Thr Cys Val Thr Asp Gly Leu Cys Phe Val
            20                  25                  30

Ser Val Thr Glu Thr Thr Asp Lys Val Ile His Asn Ser Met Cys Ile
        35                  40                  45

Ala Glu Ile Asp Leu Ile Pro Arg Asp Arg Pro Phe Val Cys Ala Pro
    50                  55                  60

Ser Ser Lys Thr Gly Ser Val Thr Thr Thr Tyr Cys Cys Asn Gln Asp
65                  70                  75                  80

His Cys Asn Lys Ile Glu Leu Pro Thr Thr Val Lys Ser Ser Pro Gly
                85                  90                  95

Leu Gly Pro Val Glu Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
            100                 105                 110

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
        115                 120                 125

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
    130                 135                 140

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

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
            180                 185                 190

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
        195                 200                 205

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
    210                 215                 220

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
225                 230                 235


<210> SEQ ID NO 62
<211> LENGTH: 262
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-TbetaRII-ED dimer T1-T2b

<400> SEQUENCE: 62

Ala Ala Leu Leu Pro Gly Ala Thr Ala Leu Gln Cys Phe Cys His Leu
1               5                   10                  15

Cys Thr Lys Asp Asn Phe Thr Cys Val Thr Asp Gly Leu Cys Phe Val
            20                  25                  30

Ser Val Thr Glu Thr Thr Asp Lys Val Ile His Asn Ser Met Cys Ile
        35                  40                  45

Ala Glu Ile Asp Leu Ile Pro Arg Asp Arg Pro Phe Val Cys Ala Pro
    50                  55                  60

Ser Ser Lys Thr Gly Ser Val Thr Thr Thr Tyr Cys Cys Asn Gln Asp
65                  70                  75                  80

His Cys Asn Lys Ile Glu Leu Pro Thr Thr Val Lys Ser Ser Pro Gly
                85                  90                  95

Leu Gly Pro Val Glu Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
            100                 105                 110

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
        115                 120                 125

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
    130                 135                 140

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
145                 150                 155                 160

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
                165                 170                 175

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
            180                 185                 190

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
        195                 200                 205

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
    210                 215                 220

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
225                 230                 235                 240

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
                245                 250                 255

Asn Thr Ser Asn Pro Asp
            260


<210> SEQ ID NO 63
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<211> LENGTH: 237
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-TbetaRII-ED dimer T2-T1

<400> SEQUENCE: 63

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
1 5 10 15

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
20 25 30

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
35 40 45

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
50 55 60

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
65 70 75 80

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
85 90 95

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
100 105 110

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
115 120 125

Glu Tyr Asn Thr Ser Asn Pro Asp Ala Ala Leu Leu Pro Gly Ala Thr
130 135 140

Ala Leu Gln Cys Phe Cys His Leu Cys Thr Lys Asp Asn Phe Thr Cys
145 150 155 160

Val Thr Asp Gly Leu Cys Phe Val Ser Val Thr Glu Thr Thr Asp Lys
165 170 175

Val Ile His Asn Ser Met Cys Ile Ala Glu Ile Asp Leu Ile Pro Arg
180 185 190

Asp Arg Pro Phe Val Cys Ala Pro Ser Ser Lys Thr Gly Ser Val Thr
195 200 205

Thr Thr Tyr Cys Cys Asn Gln Asp His Cys Asn Lys Ile Glu Leu Pro
210 215 220

Thr Thr Val Lys Ser Ser Pro Gly Leu Gly Pro Val Glu
225 230 235

<210> SEQ ID NO 64
<211> LENGTH: 373
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-TbetaRII-ED trimer T1-T2-T2

<400> SEQUENCE: 64

Ala Ala Leu Leu Pro Gly Ala Thr Ala Leu Gln Cys Phe Cys His Leu
1 5 10 15

Cys Thr Lys Asp Asn Phe Thr Cys Val Thr Asp Gly Leu Cys Phe Val
20 25 30

Ser Val Thr Glu Thr Thr Asp Lys Val Ile His Asn Ser Met Cys Ile
35 40 45

Ala Glu Ile Asp Leu Ile Pro Arg Asp Arg Pro Phe Val Cys Ala Pro
50 55 60

Ser Ser Lys Thr Gly Ser Val Thr Thr Thr Tyr Cys Cys Asn Gln Asp
65 70 75 80

His Cys Asn Lys Ile Glu Leu Pro Thr Thr Val Lys Ser Ser Pro Gly

```
                85                  90                  95

Leu Gly Pro Val Glu Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
            100                 105                 110

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
        115                 120                 125

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
    130                 135                 140

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
145                 150                 155                 160

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
                165                 170                 175

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
            180                 185                 190

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
        195                 200                 205

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
    210                 215                 220

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro
225                 230                 235                 240

His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn
                245                 250                 255

Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe
            260                 265                 270

Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr
        275                 280                 285

Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys
    290                 295                 300

Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu
305                 310                 315                 320

Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile
                325                 330                 335

Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys
            340                 345                 350

Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn
        355                 360                 365

Thr Ser Asn Pro Asp
    370


<210> SEQ ID NO 65
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-TbetaRII-ED trimer T1-T2-T2b

<400> SEQUENCE: 65

Ala Ala Leu Leu Pro Gly Ala Thr Ala Leu Gln Cys Phe Cys His Leu
1               5                   10                  15

Cys Thr Lys Asp Asn Phe Thr Cys Val Thr Asp Gly Leu Cys Phe Val
            20                  25                  30

Ser Val Thr Glu Thr Thr Asp Lys Val Ile His Asn Ser Met Cys Ile
        35                  40                  45

Ala Glu Ile Asp Leu Ile Pro Arg Asp Arg Pro Phe Val Cys Ala Pro
    50                  55                  60

Ser Ser Lys Thr Gly Ser Val Thr Thr Thr Tyr Cys Cys Asn Gln Asp
```

```
65                  70                  75                  80

His Cys Asn Lys Ile Glu Leu Pro Thr Thr Val Lys Ser Ser Pro Gly
                85                  90                  95

Leu Gly Pro Val Glu Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
            100                 105                 110

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
        115                 120                 125

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
    130                 135                 140

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
145                 150                 155                 160

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
                165                 170                 175

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
            180                 185                 190

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
        195                 200                 205

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
    210                 215                 220

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro
225                 230                 235                 240

His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile
                245                 250                 255

Ile Cys Pro Ser Cys Asn Arg Thr Ala His Pro Leu Arg His Ile Asn
            260                 265                 270

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
        275                 280                 285

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
    290                 295                 300

Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
305                 310                 315                 320

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
                325                 330                 335

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
            340                 345                 350

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
        355                 360                 365

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
    370                 375                 380

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
385                 390                 395


<210> SEQ ID NO 66
<211> LENGTH: 423
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-TbetaRII-ED trimer T1-T2-T2bAA

<400> SEQUENCE: 66

Ala Ala Leu Leu Pro Gly Ala Thr Ala Leu Gln Cys Phe Cys His Leu
1               5                   10                  15

Cys Thr Lys Asp Asn Phe Thr Cys Val Thr Asp Gly Leu Cys Phe Val
            20                  25                  30

Ser Val Thr Glu Thr Thr Asp Lys Val Ile His Asn Ser Met Cys Ile
```

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        35                  40                  45

Ala Glu Ile Asp Leu Ile Pro Arg Asp Arg Pro Phe Val Cys Ala Pro
    50                  55                  60

Ser Ser Lys Thr Gly Ser Val Thr Thr Thr Tyr Cys Cys Asn Gln Asp
65                  70                  75                  80

His Cys Asn Lys Ile Glu Leu Pro Thr Thr Val Lys Ser Ser Pro Gly
                85                  90                  95

Leu Gly Pro Val Glu Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
            100                 105                 110

Met Glu Ala Gln Lys Asp Glu Ile Ile Cys Pro Ser Cys Asn Arg Thr
        115                 120                 125

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
    130                 135                 140

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
145                 150                 155                 160

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
                165                 170                 175

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
            180                 185                 190

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
        195                 200                 205

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
    210                 215                 220

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
225                 230                 235                 240

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
                245                 250                 255

Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Asp Val
            260                 265                 270

Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro Ser Ala Asn Arg
        275                 280                 285

Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp
    290                 295                 300

Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val
305                 310                 315                 320

Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser
                325                 330                 335

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

Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro
        355                 360                 365

Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys
    370                 375                 380

Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys
385                 390                 395                 400

Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu
                405                 410                 415

Tyr Asn Thr Ser Asn Pro Asp
            420


<210> SEQ ID NO 67
<211> LENGTH: 373
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
```

<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-TbetaRII-ED trimer T2-T2-T1

<400> SEQUENCE: 67

```
Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
1               5                   10                  15

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
            20                  25                  30

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
        35                  40                  45

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
    50                  55                  60

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
65                  70                  75                  80

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
                85                  90                  95

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
            100                 105                 110

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
        115                 120                 125

Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser
    130                 135                 140

Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe
145                 150                 155                 160

Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn
                165                 170                 175

Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys
            180                 185                 190

Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile
        195                 200                 205

Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe
    210                 215                 220

Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys
225                 230                 235                 240

Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys
                245                 250                 255

Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            260                 265                 270

Ala Ala Leu Leu Pro Gly Ala Thr Ala Leu Gln Cys Phe Cys His Leu
        275                 280                 285

Cys Thr Lys Asp Asn Phe Thr Cys Val Thr Asp Gly Leu Cys Phe Val
    290                 295                 300

Ser Val Thr Glu Thr Thr Asp Lys Val Ile His Asn Ser Met Cys Ile
305                 310                 315                 320

Ala Glu Ile Asp Leu Ile Pro Arg Asp Arg Pro Phe Val Cys Ala Pro
                325                 330                 335

Ser Ser Lys Thr Gly Ser Val Thr Thr Thr Tyr Cys Cys Asn Gln Asp
            340                 345                 350

His Cys Asn Lys Ile Glu Leu Pro Thr Thr Val Lys Ser Ser Pro Gly
        355                 360                 365

Leu Gly Pro Val Glu
    370
```

<210> SEQ ID NO 68

<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: TbetaRI-TbetaRII-ED trimer T2-T2bAA-T1

<400> SEQUENCE: 68

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
1 5 10 15

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
20 25 30

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
35 40 45

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
50 55 60

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
65 70 75 80

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
85 90 95

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
100 105 110

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
115 120 125

Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser
130 135 140

Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro Ser Ala
145 150 155 160

Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val
165 170 175

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
180 185 190

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
195 200 205

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
210 215 220

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
225 230 235 240

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
245 250 255

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
260 265 270

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
275 280 285

Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ala Ala Leu Leu Pro Gly Ala
290 295 300

Thr Ala Leu Gln Cys Phe Cys His Leu Cys Thr Lys Asp Asn Phe Thr
305 310 315 320

Cys Val Thr Asp Gly Leu Cys Phe Val Ser Val Thr Glu Thr Thr Asp
325 330 335

Lys Val Ile His Asn Ser Met Cys Ile Ala Glu Ile Asp Leu Ile Pro
340 345 350

Arg Asp Arg Pro Phe Val Cys Ala Pro Ser Ser Lys Thr Gly Ser Val
355 360 365

Thr Thr Thr Tyr Cys Cys Asn Gln Asp His Cys Asn Lys Ile Glu Leu
370 375 380

```
Pro Thr Thr Val Lys Ser Ser Pro Gly Leu Gly Pro Val Glu
385                 390                 395


<210> SEQ ID NO 69
<211> LENGTH: 85
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: BMPRIa-ED structured domain

<400> SEQUENCE: 69

Thr Leu Pro Phe Leu Lys Cys Tyr Cys Ser Gly His Cys Pro Asp Asp
1               5                   10                  15

Ala Ile Asn Asn Thr Cys Ile Thr Asn Gly His Cys Phe Ala Ile Ile
            20                  25                  30

Glu Glu Asp Asp Gln Gly Glu Thr Thr Leu Ala Ser Gly Cys Met Lys
        35                  40                  45

Tyr Glu Gly Ser Asp Phe Gln Cys Lys Asp Ser Pro Lys Ala Gln Leu
    50                  55                  60

Arg Arg Thr Ile Glu Cys Cys Arg Thr Asn Leu Cys Asn Gln Tyr Leu
65                  70                  75                  80

Gln Pro Thr Leu Pro
                85


<210> SEQ ID NO 70
<211> LENGTH: 31
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: BMPRIa-ED N-term unstructured region and
      natural linker

<400> SEQUENCE: 70

Gln Asn Leu Asp Ser Met Leu His Gly Thr Gly Met Lys Ser Asp Ser
1               5                   10                  15

Asp Gln Lys Lys Ser Glu Asn Gly Val Thr Leu Ala Pro Glu Asp
            20                  25                  30


<210> SEQ ID NO 71
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: BMPRIa-ED C-term unstructured region and
      natural linker

<400> SEQUENCE: 71

Pro Val Val Ile Gly Pro Phe Phe Asp Gly Ser Ile Arg
1               5                   10


<210> SEQ ID NO 72
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: BMPRIa-ED natural linker

<400> SEQUENCE: 72

Pro Val Val Ile Gly Pro Phe Phe Asp Gly Ser Ile Arg Gln Asn Leu
1               5                   10                  15

Asp Ser Met Leu His Gly Thr Gly Met Lys Ser Asp Ser Asp Gln Lys
            20                  25                  30
```

```
Lys Ser Glu Asn Gly Val Thr Leu Ala Pro Glu Asp
        35                  40


<210> SEQ ID NO 73
<211> LENGTH: 129
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: BMPRIa-ED monomer

<400> SEQUENCE: 73

Gln Asn Leu Asp Ser Met Leu His Gly Thr Gly Met Lys Ser Asp Ser
1               5                   10                  15

Asp Gln Lys Lys Ser Glu Asn Gly Val Thr Leu Ala Pro Glu Asp Thr
            20                  25                  30

Leu Pro Phe Leu Lys Cys Tyr Cys Ser Gly His Cys Pro Asp Asp Ala
        35                  40                  45

Ile Asn Asn Thr Cys Ile Thr Asn Gly His Cys Phe Ala Ile Ile Glu
    50                  55                  60

Glu Asp Asp Gln Gly Glu Thr Thr Leu Ala Ser Gly Cys Met Lys Tyr
65                  70                  75                  80

Glu Gly Ser Asp Phe Gln Cys Lys Asp Ser Pro Lys Ala Gln Leu Arg
                85                  90                  95

Arg Thr Ile Glu Cys Cys Arg Thr Asn Leu Cys Asn Gln Tyr Leu Gln
            100                 105                 110

Pro Thr Leu Pro Pro Val Val Ile Gly Pro Phe Phe Asp Gly Ser Ile
        115                 120                 125

Arg


<210> SEQ ID NO 74
<211> LENGTH: 258
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: BMPRIa-ED dimer

<400> SEQUENCE: 74

Gln Asn Leu Asp Ser Met Leu His Gly Thr Gly Met Lys Ser Asp Ser
1               5                   10                  15

Asp Gln Lys Lys Ser Glu Asn Gly Val Thr Leu Ala Pro Glu Asp Thr
            20                  25                  30

Leu Pro Phe Leu Lys Cys Tyr Cys Ser Gly His Cys Pro Asp Asp Ala
        35                  40                  45

Ile Asn Asn Thr Cys Ile Thr Asn Gly His Cys Phe Ala Ile Ile Glu
    50                  55                  60

Glu Asp Asp Gln Gly Glu Thr Thr Leu Ala Ser Gly Cys Met Lys Tyr
65                  70                  75                  80

Glu Gly Ser Asp Phe Gln Cys Lys Asp Ser Pro Lys Ala Gln Leu Arg
                85                  90                  95

Arg Thr Ile Glu Cys Cys Arg Thr Asn Leu Cys Asn Gln Tyr Leu Gln
            100                 105                 110

Pro Thr Leu Pro Pro Val Val Ile Gly Pro Phe Phe Asp Gly Ser Ile
        115                 120                 125

Arg Gln Asn Leu Asp Ser Met Leu His Gly Thr Gly Met Lys Ser Asp
    130                 135                 140

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

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Thr Leu Pro Phe Leu Lys Cys Tyr Cys Ser Gly His Cys Pro Asp Asp
                165                 170                 175

Ala Ile Asn Asn Thr Cys Ile Thr Asn Gly His Cys Phe Ala Ile Ile
            180                 185                 190

Glu Glu Asp Asp Gln Gly Glu Thr Thr Leu Ala Ser Gly Cys Met Lys
        195                 200                 205

Tyr Glu Gly Ser Asp Phe Gln Cys Lys Asp Ser Pro Lys Ala Gln Leu
    210                 215                 220

Arg Arg Thr Ile Glu Cys Cys Arg Thr Asn Leu Cys Asn Gln Tyr Leu
225                 230                 235                 240

Gln Pro Thr Leu Pro Pro Val Val Ile Gly Pro Phe Phe Asp Gly Ser
                245                 250                 255

Ile Arg


<210> SEQ ID NO 75
<211> LENGTH: 92
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIa-ED structured domain

<400> SEQUENCE: 75

Thr Gln Glu Cys Leu Phe Phe Asn Ala Asn Trp Glu Lys Asp Arg Thr
1               5                   10                  15

Asn Gln Thr Gly Val Glu Pro Cys Tyr Gly Asp Lys Asp Lys Arg Arg
            20                  25                  30

His Cys Phe Ala Thr Trp Lys Asn Ile Ser Gly Ser Ile Glu Ile Val
        35                  40                  45

Lys Gln Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Thr Asp
    50                  55                  60

Cys Val Glu Lys Lys Asp Ser Pro Glu Val Tyr Phe Cys Cys Cys Glu
65                  70                  75                  80

Gly Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe Pro
                85                  90


<210> SEQ ID NO 76
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIa-ED N-term unstructured region and
      natural linker

<400> SEQUENCE: 76

Ala Ile Leu Gly Arg Ser Glu
1               5


<210> SEQ ID NO 77
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIa-ED C-term unstructured region and
      natural linker

<400> SEQUENCE: 77

Glu Met Glu Val Thr Gln Pro Thr Ser Asn Pro Val Thr Pro Lys Pro
1               5                   10                  15

Pro Tyr Tyr Asn Ile
            20
```

<210> SEQ ID NO 78
<211> LENGTH: 28
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIa-ED natural linker

<400> SEQUENCE: 78

Glu Met Glu Val Thr Gln Pro Thr Ser Asn Pro Val Thr Pro Lys Pro
1 5 10 15

Pro Tyr Tyr Asn Ile Ala Ile Leu Gly Arg Ser Glu
20 25

<210> SEQ ID NO 79
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIa-ED monomer

<400> SEQUENCE: 79

Ala Ile Leu Gly Arg Ser Glu Thr Gln Glu Cys Leu Phe Phe Asn Ala
1 5 10 15

Asn Trp Glu Lys Asp Arg Thr Asn Gln Thr Gly Val Glu Pro Cys Tyr
20 25 30

Gly Asp Lys Asp Lys Arg Arg His Cys Phe Ala Thr Trp Lys Asn Ile
35 40 45

Ser Gly Ser Ile Glu Ile Val Lys Gln Gly Cys Trp Leu Asp Asp Ile
50 55 60

Asn Cys Tyr Asp Arg Thr Asp Cys Val Glu Lys Lys Asp Ser Pro Glu
65 70 75 80

Val Tyr Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe Ser
85 90 95

Tyr Phe Pro Glu Met Glu Val Thr Gln Pro Thr Ser Asn Pro Val Thr
100 105 110

Pro Lys Pro Pro Tyr Tyr Asn Ile
115 120

<210> SEQ ID NO 80
<211> LENGTH: 240
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIa-ED dimer

<400> SEQUENCE: 80

Ala Ile Leu Gly Arg Ser Glu Thr Gln Glu Cys Leu Phe Phe Asn Ala
1 5 10 15

Asn Trp Glu Lys Asp Arg Thr Asn Gln Thr Gly Val Glu Pro Cys Tyr
20 25 30

Gly Asp Lys Asp Lys Arg Arg His Cys Phe Ala Thr Trp Lys Asn Ile
35 40 45

Ser Gly Ser Ile Glu Ile Val Lys Gln Gly Cys Trp Leu Asp Asp Ile
50 55 60

Asn Cys Tyr Asp Arg Thr Asp Cys Val Glu Lys Lys Asp Ser Pro Glu
65 70 75 80

Val Tyr Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe Ser
85 90 95

Tyr Phe Pro Glu Met Glu Val Thr Gln Pro Thr Ser Asn Pro Val Thr

```
            100                 105                 110

Pro Lys Pro Pro Tyr Tyr Asn Ile Ala Ile Leu Gly Arg Ser Glu Thr
        115                 120                 125

Gln Glu Cys Leu Phe Phe Asn Ala Asn Trp Glu Lys Asp Arg Thr Asn
    130                 135                 140

Gln Thr Gly Val Glu Pro Cys Tyr Gly Asp Lys Asp Lys Arg Arg His
145                 150                 155                 160

Cys Phe Ala Thr Trp Lys Asn Ile Ser Gly Ser Ile Glu Ile Val Lys
                165                 170                 175

Gln Gly Cys Trp Leu Asp Asp Ile Asn Cys Tyr Asp Arg Thr Asp Cys
            180                 185                 190

Val Glu Lys Lys Asp Ser Pro Glu Val Tyr Phe Cys Cys Cys Glu Gly
        195                 200                 205

Asn Met Cys Asn Glu Lys Phe Ser Tyr Phe Pro Glu Met Glu Val Thr
    210                 215                 220

Gln Pro Thr Ser Asn Pro Val Thr Pro Lys Pro Pro Tyr Tyr Asn Ile
225                 230                 235                 240


<210> SEQ ID NO 81
<211> LENGTH: 91
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIb-ED structured domain

<400> SEQUENCE: 81

Arg Glu Cys Ile Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn
1               5                   10                  15

Gln Ser Gly Leu Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His
            20                  25                  30

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

Lys Gly Cys Trp Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys
    50                  55                  60

Val Ala Thr Glu Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly
65                  70                  75                  80

Asn Phe Cys Asn Glu Arg Phe Thr His Leu Pro
                85                  90


<210> SEQ ID NO 82
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIb-ED N-term unstructured region and
      natural linker

<400> SEQUENCE: 82

Ser Gly Arg Gly Glu Ala Glu Thr
1               5


<210> SEQ ID NO 83
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIb-ED C-term unstructured region and
      natural linker

<400> SEQUENCE: 83
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```
Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro
1               5                   10                  15

Thr


<210> SEQ ID NO 84
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIb-ED natural linker

<400> SEQUENCE: 84

Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro Thr Ala Pro
1               5                   10                  15

Thr Ser Gly Arg Gly Glu Ala Glu Thr
            20                  25


<210> SEQ ID NO 85
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIb-ED monomer

<400> SEQUENCE: 85

Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala
1               5                   10                  15

Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45

Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60

Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
65                  70                  75                  80

Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95

His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro
            100                 105                 110

Thr Ala Pro Thr
        115


<210> SEQ ID NO 86
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIb-ED dimer

<400> SEQUENCE: 86

Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile Tyr Tyr Asn Ala
1               5                   10                  15

Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu Glu Arg Cys Glu
            20                  25                  30

Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Arg Asn Ser
        35                  40                  45

Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp Asp Phe
    50                  55                  60

Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn Pro Gln
65                  70                  75                  80
```

```
Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg Phe Thr
                85                  90                  95

His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro Pro Pro
            100                 105                 110

Thr Ala Pro Thr Ser Gly Arg Gly Glu Ala Glu Thr Arg Glu Cys Ile
        115                 120                 125

Tyr Tyr Asn Ala Asn Trp Glu Leu Glu Arg Thr Asn Gln Ser Gly Leu
    130                 135                 140

Glu Arg Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser
145                 150                 155                 160

Trp Arg Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp
                165                 170                 175

Leu Asp Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu
            180                 185                 190

Glu Asn Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn
        195                 200                 205

Glu Arg Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr
    210                 215                 220

Glu Pro Pro Pro Thr Ala Pro Thr
225                 230


<210> SEQ ID NO 87
<211> LENGTH: 52
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIa-BMPRIa-ED natural linker

<400> SEQUENCE: 87

Glu Met Glu Val Thr Gln Pro Thr Ser Asn Pro Val Thr Pro Lys Pro
1               5                   10                  15

Pro Tyr Tyr Asn Ile Gln Asn Leu Asp Ser Met Leu His Gly Thr Gly
            20                  25                  30

Met Lys Ser Asp Ser Asp Gln Lys Lys Ser Glu Asn Gly Val Thr Leu
        35                  40                  45

Ala Pro Glu Asp
    50


<210> SEQ ID NO 88
<211> LENGTH: 249
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: ActRIIa-BMPRIa-ED dimer

<400> SEQUENCE: 88

Ala Ile Leu Gly Arg Ser Glu Thr Gln Glu Cys Leu Phe Phe Asn Ala
1               5                   10                  15

Asn Trp Glu Lys Asp Arg Thr Asn Gln Thr Gly Val Glu Pro Cys Tyr
            20                  25                  30

Gly Asp Lys Asp Lys Arg Arg His Cys Phe Ala Thr Trp Lys Asn Ile
        35                  40                  45

Ser Gly Ser Ile Glu Ile Val Lys Gln Gly Cys Trp Leu Asp Asp Ile
    50                  55                  60

Asn Cys Tyr Asp Arg Thr Asp Cys Val Glu Lys Lys Asp Ser Pro Glu
65                  70                  75                  80

Val Tyr Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe Ser
```

```
                85                  90                  95

Tyr Phe Pro Glu Met Glu Val Thr Gln Pro Thr Ser Asn Pro Val Thr
            100                 105                 110

Pro Lys Pro Pro Tyr Tyr Asn Ile Gln Asn Leu Asp Ser Met Leu His
        115                 120                 125

Gly Thr Gly Met Lys Ser Asp Ser Asp Gln Lys Lys Ser Glu Asn Gly
    130                 135                 140

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

Ser Gly His Cys Pro Asp Asp Ala Ile Asn Asn Thr Cys Ile Thr Asn
                165                 170                 175

Gly His Cys Phe Ala Ile Ile Glu Glu Asp Asp Gln Gly Glu Thr Thr
            180                 185                 190

Leu Ala Ser Gly Cys Met Lys Tyr Glu Gly Ser Asp Phe Gln Cys Lys
        195                 200                 205

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

Asn Leu Cys Asn Gln Tyr Leu Gln Pro Thr Leu Pro Pro Val Val Ile
225                 230                 235                 240

Gly Pro Phe Phe Asp Gly Ser Ile Arg
                245


<210> SEQ ID NO 89
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Signal peptide

<400> SEQUENCE: 89

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Thr His Ala


<210> SEQ ID NO 90
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Signal peptide

<400> SEQUENCE: 90

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1               5                   10                  15

Gly Ala Tyr Gly
            20


<210> SEQ ID NO 91
<211> LENGTH: 352
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-deltaC-T2m fusion

<400> SEQUENCE: 91

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

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30
```

```
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

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

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

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

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His Val Gln Lys Ser
    210                 215                 220

Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe
225                 230                 235                 240

Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn
                245                 250                 255

Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys
            260                 265                 270

Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile
        275                 280                 285

Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe
    290                 295                 300

Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys
305                 310                 315                 320

Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys
                325                 330                 335

Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            340                 345                 350


<210> SEQ ID NO 92
<211> LENGTH: 356
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-C-T2m fusion

<400> SEQUENCE: 92

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
1               5                   10                  15

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            20                  25                  30

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
        35                  40                  45
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Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    50                  55                  60

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
65                  70                  75                  80

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                85                  90                  95

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            100                 105                 110

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

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    130                 135                 140

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
145                 150                 155                 160

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                165                 170                 175

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            180                 185                 190

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        195                 200                 205

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His
    210                 215                 220

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
225                 230                 235                 240

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
                245                 250                 255

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
            260                 265                 270

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
        275                 280                 285

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
    290                 295                 300

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
305                 310                 315                 320

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
                325                 330                 335

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
            340                 345                 350

Ser Asn Pro Asp
        355


<210> SEQ ID NO 93
<211> LENGTH: 362
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-CC-T2m fusion

<400> SEQUENCE: 93

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45
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Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

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

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

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
225                 230                 235                 240

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
                245                 250                 255

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
            260                 265                 270

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
        275                 280                 285

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
    290                 295                 300

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
305                 310                 315                 320

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
                325                 330                 335

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
            340                 345                 350

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        355                 360


<210> SEQ ID NO 94
<211> LENGTH: 351
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-deltaC-T2m fusion

<400> SEQUENCE: 94

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1               5                   10                  15

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            20                  25                  30

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
        35                  40                  45
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Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    50                  55                  60

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
65                  70                  75                  80

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
                85                  90                  95

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
            100                 105                 110

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        115                 120                 125

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    130                 135                 140

Asp Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145                 150                 155                 160

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                165                 170                 175

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

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        195                 200                 205

Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His Val Gln Lys Ser Val
    210                 215                 220

Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
225                 230                 235                 240

Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
                245                 250                 255

Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
            260                 265                 270

Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
        275                 280                 285

Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
    290                 295                 300

Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
305                 310                 315                 320

Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
                325                 330                 335

Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            340                 345                 350


<210> SEQ ID NO 95
<211> LENGTH: 355
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-C-T2m fusion

<400> SEQUENCE: 95

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
1               5                   10                  15

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
            20                  25                  30

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
        35                  40                  45

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
    50                  55                  60
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Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr
65                  70                  75                  80

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
                85                  90                  95

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
            100                 105                 110

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
        115                 120                 125

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
    130                 135                 140

Phe Tyr Pro Ser Asp Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro
145                 150                 155                 160

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
                165                 170                 175

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
            180                 185                 190

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
        195                 200                 205

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His Val
    210                 215                 220

Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala
225                 230                 235                 240

Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr
                245                 250                 255

Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile
            260                 265                 270

Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp
        275                 280                 285

Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr
    290                 295                 300

His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys
305                 310                 315                 320

Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser
                325                 330                 335

Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser
            340                 345                 350

Asn Pro Asp
        355


<210> SEQ ID NO 96
<211> LENGTH: 351
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-CC-T2m fusion

<400> SEQUENCE: 96

Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1               5                   10                  15

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            20                  25                  30

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
        35                  40                  45

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    50                  55                  60
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Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
65                  70                  75                  80

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
                85                  90                  95

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
            100                 105                 110

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        115                 120                 125

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    130                 135                 140

Asp Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145                 150                 155                 160

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                165                 170                 175

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

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        195                 200                 205

Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His Val Gln Lys Ser Val
    210                 215                 220

Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
225                 230                 235                 240

Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
                245                 250                 255

Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
            260                 265                 270

Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
        275                 280                 285

Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
    290                 295                 300

Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
305                 310                 315                 320

Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
                325                 330                 335

Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            340                 345                 350


<210> SEQ ID NO 97
<211> LENGTH: 383
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2Fc-CCCC-T2 fusion, also termed Fc-T2m

<400> SEQUENCE: 97

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Thr His Ala Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
            20                  25                  30

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        35                  40                  45

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    50                  55                  60

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
65                  70                  75                  80
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```
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                85                  90                  95

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
            100                 105                 110

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        115                 120                 125

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
    130                 135                 140

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
145                 150                 155                 160

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                165                 170                 175

Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            180                 185                 190

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        195                 200                 205

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
    210                 215                 220

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
225                 230                 235                 240

Leu Ser Leu Ser Pro Gly Lys Ile Pro Pro His Val Gln Lys Ser Val
                245                 250                 255

Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
            260                 265                 270

Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
        275                 280                 285

Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
    290                 295                 300

Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
305                 310                 315                 320

Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
                325                 330                 335

Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
            340                 345                 350

Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
        355                 360                 365

Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
    370                 375                 380


<210> SEQ ID NO 98
<211> LENGTH: 364
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4Fc K-CC-228P-T2m fusion

<400> SEQUENCE: 98

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60
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Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
225                 230                 235                 240

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
                245                 250                 255

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
            260                 265                 270

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
        275                 280                 285

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
    290                 295                 300

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
305                 310                 315                 320

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
                325                 330                 335

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
            340                 345                 350

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        355                 360


<210> SEQ ID NO 99
<211> LENGTH: 364
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P-409K-T2m fusion

<400> SEQUENCE: 99

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60
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Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
225                 230                 235                 240

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
                245                 250                 255

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
            260                 265                 270

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
        275                 280                 285

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
    290                 295                 300

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
305                 310                 315                 320

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
                325                 330                 335

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
            340                 345                 350

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        355                 360


<210> SEQ ID NO 100
<211> LENGTH: 492
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-C-T22d35 fusion

<400> SEQUENCE: 100

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
1               5                   10                  15

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            20                  25                  30

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
        35                  40                  45

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    50                  55                  60
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Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
65                  70                  75                  80

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                85                  90                  95

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            100                 105                 110

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

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    130                 135                 140

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
145                 150                 155                 160

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                165                 170                 175

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            180                 185                 190

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        195                 200                 205

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His
    210                 215                 220

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
225                 230                 235                 240

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
                245                 250                 255

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
            260                 265                 270

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
        275                 280                 285

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
    290                 295                 300

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
305                 310                 315                 320

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
                325                 330                 335

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
            340                 345                 350

Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
        355                 360                 365

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
    370                 375                 380

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
385                 390                 395                 400

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
                405                 410                 415

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
            420                 425                 430

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
        435                 440                 445

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
    450                 455                 460

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
465                 470                 475                 480

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
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                485                 490


<210> SEQ ID NO 101
<211> LENGTH: 498
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-CC-T22d35 fusion

<400> SEQUENCE: 101

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

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

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

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
225                 230                 235                 240

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
                245                 250                 255

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
            260                 265                 270

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
        275                 280                 285

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
    290                 295                 300

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
305                 310                 315                 320

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
                325                 330                 335

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
            340                 345                 350

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln
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        355                 360                 365

Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val
    370                 375                 380

Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys
385                 390                 395                 400

Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys
                405                 410                 415

Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu
            420                 425                 430

Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His
        435                 440                 445

Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu
    450                 455                 460

Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp
465                 470                 475                 480

Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn
                485                 490                 495

Pro Asp


<210> SEQ ID NO 102
<211> LENGTH: 494
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-CC-T22d35 fusion

<400> SEQUENCE: 102

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
1               5                   10                  15

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            20                  25                  30

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        35                  40                  45

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    50                  55                  60

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
65                  70                  75                  80

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                85                  90                  95

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            100                 105                 110

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
        115                 120                 125

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    130                 135                 140

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

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                165                 170                 175

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            180                 185                 190

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        195                 200                 205

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

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                245                 250                 255

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            260                 265                 270

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        275                 280                 285

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    290                 295                 300

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
305                 310                 315                 320

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                325                 330                 335

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            340                 345                 350

Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn
        355                 360                 365

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
    370                 375                 380

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
385                 390                 395                 400

Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
                405                 410                 415

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
            420                 425                 430

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
        435                 440                 445

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
    450                 455                 460

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
465                 470                 475                 480

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
                485                 490


<210> SEQ ID NO 103
<211> LENGTH: 500
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P-T22d35 fusion

<400> SEQUENCE: 103

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95
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Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
225                 230                 235                 240

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
                245                 250                 255

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
            260                 265                 270

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
        275                 280                 285

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
    290                 295                 300

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
305                 310                 315                 320

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
                325                 330                 335

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
            340                 345                 350

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His
        355                 360                 365

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
    370                 375                 380

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
385                 390                 395                 400

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
                405                 410                 415

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
            420                 425                 430

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
        435                 440                 445

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
    450                 455                 460

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
465                 470                 475                 480

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
                485                 490                 495

Ser Asn Pro Asp
            500
```

<210> SEQ ID NO 104
<211> LENGTH: 500
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P-409K-T22d35 fusion

<400> SEQUENCE: 104

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
180 185 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
195 200 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
210 215 220

Leu Ser Leu Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
225 230 235 240

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
245 250 255

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
260 265 270

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
275 280 285

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
290 295 300

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
305 310 315 320

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
325 330 335

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
340 345 350

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His
355 360 365

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Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
    370                 375                 380

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
385                 390                 395                 400

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
                405                 410                 415

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
            420                 425                 430

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
        435                 440                 445

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
    450                 455                 460

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
465                 470                 475                 480

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
                485                 490                 495

Ser Asn Pro Asp
            500


<210> SEQ ID NO 105
<211> LENGTH: 519
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2Fc-CCCC-T22d35 fusion, also termed
      Fc-T22d35

<400> SEQUENCE: 105

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Thr His Ala Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
            20                  25                  30

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        35                  40                  45

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    50                  55                  60

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
65                  70                  75                  80

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                85                  90                  95

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
            100                 105                 110

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        115                 120                 125

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
    130                 135                 140

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
145                 150                 155                 160

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                165                 170                 175

Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            180                 185                 190

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        195                 200                 205

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

Leu Ser Leu Ser Pro Gly Lys Ile Pro Pro His Val Gln Lys Ser Val
                245                 250                 255

Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
            260                 265                 270

Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
        275                 280                 285

Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
    290                 295                 300

Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
305                 310                 315                 320

Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
                325                 330                 335

Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
            340                 345                 350

Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
        355                 360                 365

Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile
    370                 375                 380

Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp
385                 390                 395                 400

Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val
                405                 410                 415

Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser
            420                 425                 430

Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp
        435                 440                 445

Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro
    450                 455                 460

Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys
465                 470                 475                 480

Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys
                485                 490                 495

Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu
            500                 505                 510

Tyr Asn Thr Ser Asn Pro Asp
        515


<210> SEQ ID NO 106
<211> LENGTH: 517
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-C-T2-T2bAA fusion

<400> SEQUENCE: 106

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
1               5                   10                  15

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            20                  25                  30

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
        35                  40                  45

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    50                  55                  60
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```
Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
65                  70                  75                  80

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                85                  90                  95

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            100                 105                 110

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

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    130                 135                 140

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
145                 150                 155                 160

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                165                 170                 175

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            180                 185                 190

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        195                 200                 205

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His
    210                 215                 220

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
225                 230                 235                 240

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
                245                 250                 255

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
            260                 265                 270

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
        275                 280                 285

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
    290                 295                 300

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
305                 310                 315                 320

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
                325                 330                 335

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
            340                 345                 350

Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met
        355                 360                 365

Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro Ser Ala Asn Arg Thr Ala
    370                 375                 380

His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn
385                 390                 395                 400

Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe
                405                 410                 415

Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr
            420                 425                 430

Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys
        435                 440                 445

Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu
    450                 455                 460

Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile
465                 470                 475                 480
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```
Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys
                485                 490                 495

Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn
            500                 505                 510

Thr Ser Asn Pro Asp
        515


<210> SEQ ID NO 107
<211> LENGTH: 523
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-CC-T2-T2bAA fusion

<400> SEQUENCE: 107

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

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

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

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
225                 230                 235                 240

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
                245                 250                 255

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
            260                 265                 270

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
        275                 280                 285

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
    290                 295                 300

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
305                 310                 315                 320
```

```
Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
                325                 330                 335

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
            340                 345                 350

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln
        355                 360                 365

Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro
    370                 375                 380

Ser Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met
385                 390                 395                 400

Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys
                405                 410                 415

Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met
            420                 425                 430

Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys
        435                 440                 445

Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val
    450                 455                 460

Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala
465                 470                 475                 480

Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr
                485                 490                 495

Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile
            500                 505                 510

Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        515                 520


<210> SEQ ID NO 108
<211> LENGTH: 519
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-CC-T2-T2bAA fusion

<400> SEQUENCE: 108

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
1               5                   10                  15

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            20                  25                  30

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        35                  40                  45

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    50                  55                  60

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
65                  70                  75                  80

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                85                  90                  95

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            100                 105                 110

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
        115                 120                 125

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    130                 135                 140

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ser Val Glu Trp Glu Ser Asn
145                 150                 155                 160
```

```
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                165                 170                 175

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            180                 185                 190

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        195                 200                 205

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro
    210                 215                 220

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
225                 230                 235                 240

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                245                 250                 255

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            260                 265                 270

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        275                 280                 285

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    290                 295                 300

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
305                 310                 315                 320

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                325                 330                 335

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            340                 345                 350

Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Asp Val
        355                 360                 365

Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro Ser Ala Asn Arg
    370                 375                 380

Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp
385                 390                 395                 400

Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val
                405                 410                 415

Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser
            420                 425                 430

Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp
        435                 440                 445

Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro
    450                 455                 460

Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys
465                 470                 475                 480

Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys
                485                 490                 495

Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu
            500                 505                 510

Tyr Asn Thr Ser Asn Pro Asp
        515


<210> SEQ ID NO 109
<211> LENGTH: 525
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P-T2-T2bAA fusion

<400> SEQUENCE: 109
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```
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
225                 230                 235                 240

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
                245                 250                 255

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
            260                 265                 270

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
        275                 280                 285

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
    290                 295                 300

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
305                 310                 315                 320

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
                325                 330                 335

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
            340                 345                 350

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His
        355                 360                 365

Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile
    370                 375                 380

Ala Pro Ser Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn
385                 390                 395                 400

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
                405                 410                 415

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
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            420                 425                 430

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
        435                 440                 445

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
    450                 455                 460

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
465                 470                 475                 480

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
                485                 490                 495

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
            500                 505                 510

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        515                 520                 525


<210> SEQ ID NO 110
<211> LENGTH: 525
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P-409K-T2-T2bAA fusion

<400> SEQUENCE: 110

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
225                 230                 235                 240

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
                245                 250                 255

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
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            260                 265                 270

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
        275                 280                 285

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
    290                 295                 300

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
305                 310                 315                 320

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
                325                 330                 335

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
            340                 345                 350

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His
        355                 360                 365

Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile
    370                 375                 380

Ala Pro Ser Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn
385                 390                 395                 400

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
                405                 410                 415

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
            420                 425                 430

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
        435                 440                 445

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
    450                 455                 460

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
465                 470                 475                 480

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
                485                 490                 495

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
            500                 505                 510

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        515                 520                 525


<210> SEQ ID NO 111
<211> LENGTH: 628
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-C-T2-T2-T2 fusion

<400> SEQUENCE: 111

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
1               5                   10                  15

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            20                  25                  30

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
        35                  40                  45

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    50                  55                  60

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
65                  70                  75                  80

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                85                  90                  95

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
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            100                 105                 110

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

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    130                 135                 140

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
145                 150                 155                 160

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                165                 170                 175

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            180                 185                 190

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        195                 200                 205

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His
    210                 215                 220

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
225                 230                 235                 240

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
                245                 250                 255

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
            260                 265                 270

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
        275                 280                 285

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
    290                 295                 300

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
305                 310                 315                 320

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
                325                 330                 335

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
            340                 345                 350

Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
        355                 360                 365

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
    370                 375                 380

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
385                 390                 395                 400

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
                405                 410                 415

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
            420                 425                 430

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
        435                 440                 445

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
    450                 455                 460

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
465                 470                 475                 480

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His
                485                 490                 495

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
            500                 505                 510

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
        515                 520                 525
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Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
    530                 535                 540

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
545                 550                 555                 560

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
                565                 570                 575

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
            580                 585                 590

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
        595                 600                 605

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
    610                 615                 620

Ser Asn Pro Asp
625


<210> SEQ ID NO 112
<211> LENGTH: 634
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-CC-T2-T2-T2 fusion

<400> SEQUENCE: 112

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

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

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

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
225                 230                 235                 240

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
                245                 250                 255
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Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
            260                 265                 270

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
        275                 280                 285

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
    290                 295                 300

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
305                 310                 315                 320

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
                325                 330                 335

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
            340                 345                 350

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln
        355                 360                 365

Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val
    370                 375                 380

Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys
385                 390                 395                 400

Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys
                405                 410                 415

Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu
            420                 425                 430

Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His
        435                 440                 445

Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu
    450                 455                 460

Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp
465                 470                 475                 480

Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn
                485                 490                 495

Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
            500                 505                 510

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
        515                 520                 525

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
    530                 535                 540

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
545                 550                 555                 560

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
                565                 570                 575

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
            580                 585                 590

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
        595                 600                 605

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
    610                 615                 620

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
625                 630
```

<210> SEQ ID NO 113
<211> LENGTH: 630
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

<223> OTHER INFORMATION: hIgG2FcdeltaK-CC-T2-T2-T2 fusion

<400> SEQUENCE: 113

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Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
1               5                   10                  15

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            20                  25                  30

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        35                  40                  45

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    50                  55                  60

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
65                  70                  75                  80

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                85                  90                  95

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            100                 105                 110

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
        115                 120                 125

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    130                 135                 140

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

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                165                 170                 175

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            180                 185                 190

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        195                 200                 205

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro
    210                 215                 220

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
225                 230                 235                 240

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                245                 250                 255

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            260                 265                 270

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        275                 280                 285

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    290                 295                 300

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
305                 310                 315                 320

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                325                 330                 335

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            340                 345                 350

Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn
        355                 360                 365

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
    370                 375                 380

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
385                 390                 395                 400
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Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
                405                 410                 415

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
            420                 425                 430

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
        435                 440                 445

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
    450                 455                 460

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
465                 470                 475                 480

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro
                485                 490                 495

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
            500                 505                 510

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
        515                 520                 525

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
    530                 535                 540

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
545                 550                 555                 560

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
                565                 570                 575

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
            580                 585                 590

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
        595                 600                 605

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
    610                 615                 620

Asn Thr Ser Asn Pro Asp
625                 630


<210> SEQ ID NO 114
<211> LENGTH: 636
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P-T2-T2-T2 fusion

<400> SEQUENCE: 114

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125
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Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
225                 230                 235                 240

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
                245                 250                 255

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
            260                 265                 270

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
        275                 280                 285

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
    290                 295                 300

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
305                 310                 315                 320

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
                325                 330                 335

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
            340                 345                 350

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His
        355                 360                 365

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
    370                 375                 380

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
385                 390                 395                 400

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
                405                 410                 415

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
            420                 425                 430

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
        435                 440                 445

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
    450                 455                 460

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
465                 470                 475                 480

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
                485                 490                 495

Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
            500                 505                 510

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
        515                 520                 525

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
    530                 535                 540

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
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545                 550                 555                 560

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
                565                 570                 575

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
            580                 585                 590

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
        595                 600                 605

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
    610                 615                 620

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
625                 630                 635


<210> SEQ ID NO 115
<211> LENGTH: 636
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P-409K-T2-T2-T2 fusion

<400> SEQUENCE: 115

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                   10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
225                 230                 235                 240

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
                245                 250                 255

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
            260                 265                 270

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
```

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        275                 280                 285

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
    290                 295                 300

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
305                 310                 315                 320

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
                325                 330                 335

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
            340                 345                 350

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His
        355                 360                 365

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
    370                 375                 380

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
385                 390                 395                 400

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
                405                 410                 415

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
            420                 425                 430

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
        435                 440                 445

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
    450                 455                 460

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
465                 470                 475                 480

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
                485                 490                 495

Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
            500                 505                 510

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
        515                 520                 525

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
    530                 535                 540

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
545                 550                 555                 560

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
                565                 570                 575

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
            580                 585                 590

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
        595                 600                 605

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
    610                 615                 620

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
625                 630                 635


<210> SEQ ID NO 116
<211> LENGTH: 678
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-C-T2-T2bAA-T2bAA fusion

<400> SEQUENCE: 116

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
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1               5                   10                  15

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
            20                  25                  30

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
        35                  40                  45

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
    50                  55                  60

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
65                  70                  75                  80

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
                85                  90                  95

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            100                 105                 110

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

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
    130                 135                 140

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
145                 150                 155                 160

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
                165                 170                 175

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
            180                 185                 190

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
        195                 200                 205

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His
    210                 215                 220

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
225                 230                 235                 240

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
                245                 250                 255

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
            260                 265                 270

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
        275                 280                 285

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
    290                 295                 300

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
305                 310                 315                 320

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
                325                 330                 335

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
            340                 345                 350

Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Asp Val Glu Met
        355                 360                 365

Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro Ser Ala Asn Arg Thr Ala
    370                 375                 380

His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn Asn
385                 390                 395                 400

Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe
                405                 410                 415

Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr
            420                 425                 430
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Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys
        435                 440                 445

Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu
    450                 455                 460

Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile
465                 470                 475                 480

Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys
                485                 490                 495

Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn
            500                 505                 510

Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Asp Val Glu
        515                 520                 525

Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro Ser Ala Asn Arg Thr
    530                 535                 540

Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp Asn
545                 550                 555                 560

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                565                 570                 575

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            580                 585                 590

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        595                 600                 605

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    610                 615                 620

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
625                 630                 635                 640

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                645                 650                 655

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            660                 665                 670

Asn Thr Ser Asn Pro Asp
        675


<210> SEQ ID NO 117
<211> LENGTH: 684
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG1FcdeltaK-CC-T2-T2bAA-T2bAA fusion

<400> SEQUENCE: 117

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110
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```
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    130                 135                 140

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

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

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
225                 230                 235                 240

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
                245                 250                 255

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
            260                 265                 270

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
        275                 280                 285

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
    290                 295                 300

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
305                 310                 315                 320

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
                325                 330                 335

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
            340                 345                 350

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln
        355                 360                 365

Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro
    370                 375                 380

Ser Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met
385                 390                 395                 400

Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys
                405                 410                 415

Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met
            420                 425                 430

Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys
        435                 440                 445

Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val
    450                 455                 460

Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala
465                 470                 475                 480

Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr
                485                 490                 495

Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile
            500                 505                 510

Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val
        515                 520                 525
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Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala
    530                 535                 540

Pro Ser Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp
545                 550                 555                 560

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
                565                 570                 575

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
            580                 585                 590

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
        595                 600                 605

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
    610                 615                 620

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
625                 630                 635                 640

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
                645                 650                 655

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
            660                 665                 670

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        675                 680


<210> SEQ ID NO 118
<211> LENGTH: 680
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG2FcdeltaK-CC-T2-T2bAA-T2bAA fusion

<400> SEQUENCE: 118

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
1               5                   10                  15

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            20                  25                  30

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        35                  40                  45

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    50                  55                  60

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
65                  70                  75                  80

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                85                  90                  95

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            100                 105                 110

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
        115                 120                 125

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    130                 135                 140

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

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                165                 170                 175

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            180                 185                 190

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        195                 200                 205
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His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro
    210                 215                 220

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
225                 230                 235                 240

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
                245                 250                 255

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
            260                 265                 270

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
        275                 280                 285

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
    290                 295                 300

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
305                 310                 315                 320

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
                325                 330                 335

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
            340                 345                 350

Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Asp Val
        355                 360                 365

Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro Ser Ala Asn Arg
    370                 375                 380

Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr Asp
385                 390                 395                 400

Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val
                405                 410                 415

Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser
            420                 425                 430

Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp
        435                 440                 445

Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro
    450                 455                 460

Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys
465                 470                 475                 480

Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys
                485                 490                 495

Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu
            500                 505                 510

Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Asp
        515                 520                 525

Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile Ala Pro Ser Ala Asn
    530                 535                 540

Arg Thr Ala His Pro Leu Arg His Ile Asn Asn Asp Met Ile Val Thr
545                 550                 555                 560

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
                565                 570                 575

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
            580                 585                 590

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
        595                 600                 605

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
    610                 615                 620

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
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625 630 635 640

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
645 650 655

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
660 665 670

Glu Tyr Asn Thr Ser Asn Pro Asp
675 680

<210> SEQ ID NO 119
<211> LENGTH: 686
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P-T2-T2bAA-T2bAA fusion

<400> SEQUENCE: 119

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
180 185 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
195 200 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
210 215 220

Leu Ser Leu Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
225 230 235 240

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
245 250 255

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
260 265 270

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
275 280 285

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
290 295 300

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp

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305                 310                 315                 320

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
                325                 330                 335

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
            340                 345                 350

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His
        355                 360                 365

Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile
    370                 375                 380

Ala Pro Ser Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn
385                 390                 395                 400

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
                405                 410                 415

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
            420                 425                 430

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
        435                 440                 445

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
    450                 455                 460

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
465                 470                 475                 480

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
                485                 490                 495

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
            500                 505                 510

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro
        515                 520                 525

His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile
    530                 535                 540

Ile Ala Pro Ser Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn
545                 550                 555                 560

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
                565                 570                 575

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
            580                 585                 590

Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
        595                 600                 605

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
    610                 615                 620

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
625                 630                 635                 640

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
                645                 650                 655

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
            660                 665                 670

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        675                 680                 685


<210> SEQ ID NO 120
<211> LENGTH: 686
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: hIgG4FcdeltaK-CC-228P-409K-T2-T2bAA-T2bAA
      fusion
```

<400> SEQUENCE: 120

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
180 185 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
195 200 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
210 215 220

Leu Ser Leu Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
225 230 235 240

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
245 250 255

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
260 265 270

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
275 280 285

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
290 295 300

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
305 310 315 320

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
325 330 335

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
340 345 350

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His
355 360 365

Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile Ile
370 375 380

Ala Pro Ser Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn Asn
385 390 395 400

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu

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                405                 410                 415

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
            420                 425                 430

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
        435                 440                 445

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
    450                 455                 460

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
465                 470                 475                 480

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
                485                 490                 495

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
            500                 505                 510

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro
        515                 520                 525

His Val Gln Lys Ser Asp Val Glu Met Glu Ala Gln Lys Asp Glu Ile
    530                 535                 540

Ile Ala Pro Ser Ala Asn Arg Thr Ala His Pro Leu Arg His Ile Asn
545                 550                 555                 560

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
                565                 570                 575

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
            580                 585                 590

Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
        595                 600                 605

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
    610                 615                 620

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
625                 630                 635                 640

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
                645                 650                 655

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
            660                 665                 670

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        675                 680                 685


<210> SEQ ID NO 121
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cetuximab LC

<400> SEQUENCE: 121

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

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
            20                  25                  30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35                  40                  45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
65                  70                  75                  80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
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                85                  90                  95

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 122
<211> LENGTH: 721
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cetuximab HC-T22d35

<400> SEQUENCE: 122

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

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
            20                  25                  30

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

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

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

Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
                85                  90                  95

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

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

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

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

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

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

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
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225                 230                 235                 240

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val
    450                 455                 460

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
465                 470                 475                 480

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
                485                 490                 495

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
            500                 505                 510

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
        515                 520                 525

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
    530                 535                 540

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
545                 550                 555                 560

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
                565                 570                 575

Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys
            580                 585                 590

Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys
        595                 600                 605

Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp
    610                 615                 620

Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu
625                 630                 635                 640

Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn
                645                 650                 655
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Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp
            660                 665                 670

Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys
        675                 680                 685

Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu
    690                 695                 700

Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro
705                 710                 715                 720

Asp


<210> SEQ ID NO 123
<211> LENGTH: 585
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cetuximab HC-T2m

<400> SEQUENCE: 123

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

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
            20                  25                  30

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

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

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

Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
                85                  90                  95

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

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

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

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

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

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

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

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

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

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285
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Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

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

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

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

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

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

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

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

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

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

Lys Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val
    450                 455                 460

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
465                 470                 475                 480

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
                485                 490                 495

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
            500                 505                 510

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
        515                 520                 525

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
    530                 535                 540

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
545                 550                 555                 560

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
                565                 570                 575

Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            580                 585


<210> SEQ ID NO 124
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Herceptin LC

<400> SEQUENCE: 124

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
            20                  25                  30

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
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Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85                  90                  95

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 125
<211> LENGTH: 722
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Herceptin HC-T22d35

<400> SEQUENCE: 125

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

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

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

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

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

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

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

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

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

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

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
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Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Lys Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile
    450                 455                 460

Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe
465                 470                 475                 480

Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser
                485                 490                 495

Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val
            500                 505                 510

Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys
        515                 520                 525

His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala
    530                 535                 540

Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe
545                 550                 555                 560

Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe
                565                 570                 575

Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln
            580                 585                 590

Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val
        595                 600                 605

Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys
    610                 615                 620

Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys
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625 630 635 640

Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu
645 650 655

Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His
660 665 670

Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu
675 680 685

Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp
690 695 700

Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn
705 710 715 720

Pro Asp

<210> SEQ ID NO 126
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Avastin LC

<400> SEQUENCE: 126

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

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

Tyr Phe Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Thr Val Pro Trp
85 90 95

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 127
<211> LENGTH: 725
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Avastin HC-T22d35

<400> SEQUENCE: 127

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

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

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

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Ala Asp Phe
50 55 60

Lys Arg Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser Thr Ala Tyr
65 70 75 80

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

Ala Lys Tyr Pro His Tyr Tyr Gly Ser Ser His Trp Tyr Phe Asp Val
100 105 110

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

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

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

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

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

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
195 200 205

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

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225 230 235 240

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

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

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

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

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

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

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

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
355 360 365

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

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

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

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

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

Leu Ser Pro Gly Lys Ile Pro Pro His Val Gln Lys Ser Val Asn Asn
    450                 455                 460

Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu
465                 470                 475                 480

Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser
                485                 490                 495

Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu
            500                 505                 510

Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu
        515                 520                 525

Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu
    530                 535                 540

Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly
545                 550                 555                 560

Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn
                565                 570                 575

Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro
            580                 585                 590

His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn
        595                 600                 605

Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe
    610                 615                 620

Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr
625                 630                 635                 640

Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys
                645                 650                 655

Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu
            660                 665                 670

Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile
        675                 680                 685

Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys
    690                 695                 700

Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn
705                 710                 715                 720

Thr Ser Asn Pro Asp
                725


<210> SEQ ID NO 128
<211> LENGTH: 213
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synagis LC

<400> SEQUENCE: 128

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Cys Gln Leu Ser Val Gly Tyr Met
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        35                  40                  45
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Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

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

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
                85                  90                  95

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

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

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

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

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

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

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

Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 129
<211> LENGTH: 721
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synagis HC-T22d35

<400> SEQUENCE: 129

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30

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

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser
    50                  55                  60

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

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

Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Ala
            100                 105                 110

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

Phe Pro Leu Ala Pro Ser Ser Ala Ala Ala Ala Gly Gly Thr Ala Ala
    130                 135                 140

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

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

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190
```

```
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

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

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val
    450                 455                 460

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
465                 470                 475                 480

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
                485                 490                 495

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
            500                 505                 510

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
        515                 520                 525

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
    530                 535                 540

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
545                 550                 555                 560

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
                565                 570                 575

Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys
            580                 585                 590

Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys
        595                 600                 605
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Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp
    610                 615                 620

Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu
625                 630                 635                 640

Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn
                645                 650                 655

Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp
            660                 665                 670

Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys
        675                 680                 685

Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu
    690                 695                 700

Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro
705                 710                 715                 720

Asp


<210> SEQ ID NO 130
<211> LENGTH: 630
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FC5-Fc-T22d35

<400> SEQUENCE: 130

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

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

Thr Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
        35                  40                  45

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

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

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

Ala Ala Gly Ser Thr Ser Thr Ala Thr Pro Leu Arg Val Asp Tyr Trp
            100                 105                 110

Gly Lys Gly Thr Gln Val Thr Val Ser Ser Ala Ser Glu Pro Arg Gly
        115                 120                 125

Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu
    130                 135                 140

Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val
145                 150                 155                 160

Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val
                165                 170                 175

Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val
            180                 185                 190

Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser
        195                 200                 205

Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met
    210                 215                 220

Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala
225                 230                 235                 240

Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro
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                245                 250                 255

Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln
            260                 265                 270

Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr
        275                 280                 285

Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr
    290                 295                 300

Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu
305                 310                 315                 320

Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser
                325                 330                 335

Val Val His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser
            340                 345                 350

Arg Thr Pro Gly Thr Gly Ile Pro Pro His Val Gln Lys Ser Val Asn
        355                 360                 365

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
    370                 375                 380

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
385                 390                 395                 400

Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
                405                 410                 415

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
            420                 425                 430

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
        435                 440                 445

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
    450                 455                 460

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
465                 470                 475                 480

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro
                485                 490                 495

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
            500                 505                 510

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
        515                 520                 525

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
    530                 535                 540

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
545                 550                 555                 560

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
                565                 570                 575

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
            580                 585                 590

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
        595                 600                 605

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
    610                 615                 620

Asn Thr Ser Asn Pro Asp
625                 630
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<210> SEQ ID NO 131
<211> LENGTH: 494
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: FC5-Fc-T2m

<400> SEQUENCE: 131

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

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

Thr Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

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

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

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

Ala Ala Gly Ser Thr Ser Thr Ala Thr Pro Leu Arg Val Asp Tyr Trp
100 105 110

Gly Lys Gly Thr Gln Val Thr Val Ser Ser Ala Ser Glu Pro Arg Gly
115 120 125

Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu
130 135 140

Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val
145 150 155 160

Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val
165 170 175

Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val
180 185 190

Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser
195 200 205

Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met
210 215 220

Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala
225 230 235 240

Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro
245 250 255

Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln
260 265 270

Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr
275 280 285

Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr
290 295 300

Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu
305 310 315 320

Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser
325 330 335

Val Val His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser
340 345 350

Arg Thr Pro Gly Thr Gly Ile Pro Pro His Val Gln Lys Ser Val Asn
355 360 365

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
370 375 380

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
385 390 395 400

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Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
                405                 410                 415

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
            420                 425                 430

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
        435                 440                 445

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
    450                 455                 460

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
465                 470                 475                 480

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
                485                 490


<210> SEQ ID NO 132
<211> LENGTH: 392
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: T2-hIgG1Fc fusion from R&D, also termed T2m-Fc
      (R&D)

<400> SEQUENCE: 132

Met Gly Arg Gly Leu Leu Arg Gly Leu Trp Pro Leu His Ile Val Leu
1               5                   10                  15

Trp Thr Arg Ile Ala Ser Thr Ile Pro Pro His Val Gln Lys Ser Val
            20                  25                  30

Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro
        35                  40                  45

Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln
    50                  55                  60

Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro
65                  70                  75                  80

Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr
                85                  90                  95

Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile
            100                 105                 110

Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys
        115                 120                 125

Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn
    130                 135                 140

Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Met
145                 150                 155                 160

Asp Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
                165                 170                 175

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            180                 185                 190

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        195                 200                 205

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    210                 215                 220

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
225                 230                 235                 240

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                245                 250                 255

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
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            260                 265                 270

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        275                 280                 285

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    290                 295                 300

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
305                 310                 315                 320

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                325                 330                 335

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            340                 345                 350

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        355                 360                 365

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    370                 375                 380

Ser Leu Ser Leu Ser Pro Gly Lys
385                 390


<210> SEQ ID NO 133
<211> LENGTH: 382
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: T2-hIgG2Fc-CCCC fusion, also termed T2m-Fc

<400> SEQUENCE: 133

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Thr His Ala Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met
            20                  25                  30

Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys
        35                  40                  45

Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met
    50                  55                  60

Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys
65                  70                  75                  80

Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val
                85                  90                  95

Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala
            100                 105                 110

Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr
        115                 120                 125

Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile
    130                 135                 140

Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Glu Arg Lys Cys Cys
145                 150                 155                 160

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
                165                 170                 175

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            180                 185                 190

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        195                 200                 205

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    210                 215                 220

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser
```

```
225                 230                 235                 240

Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                245                 250                 255

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
            260                 265                 270

Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
        275                 280                 285

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    290                 295                 300

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

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
                325                 330                 335

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            340                 345                 350

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        355                 360                 365

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    370                 375                 380


<210> SEQ ID NO 134
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Isotope-labelled peptide for T22d35

<400> SEQUENCE: 134

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys
1               5                   10                  15


<210> SEQ ID NO 135
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Isotope-labelled peptide for Cetuximab

<400> SEQUENCE: 135

Ala Leu Pro Ala Pro Ile Glu Lys
1               5


<210> SEQ ID NO 136
<211> LENGTH: 372
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG1FcdeltaK-CC-T2m fusion

<400> SEQUENCE: 136

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Lys Thr His Thr Cys
1               5                   10                  15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
            20                  25                  30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
        35                  40                  45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
    50                  55                  60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65                  70                  75                  80
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Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
                85                  90                  95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
            100                 105                 110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
        115                 120                 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
    130                 135                 140

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145                 150                 155                 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
                165                 170                 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
            180                 185                 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
        195                 200                 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
    210                 215                 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His
225                 230                 235                 240

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
                245                 250                 255

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
            260                 265                 270

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
        275                 280                 285

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
    290                 295                 300

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
305                 310                 315                 320

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
                325                 330                 335

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
            340                 345                 350

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
        355                 360                 365

Ser Asn Pro Asp
    370


<210> SEQ ID NO 137
<211> LENGTH: 376
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-G3S-hIgG1FcdeltaK-CC-T2m fusion

<400> SEQUENCE: 137

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Gly Gly Gly Ser Asp Lys
1               5                   10                  15

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
            20                  25                  30

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        35                  40                  45

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    50                  55                  60
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Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
65                  70                  75                  80

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                85                  90                  95

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            100                 105                 110

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
        115                 120                 125

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    130                 135                 140

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
145                 150                 155                 160

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                165                 170                 175

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            180                 185                 190

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        195                 200                 205

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    210                 215                 220

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
225                 230                 235                 240

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
                245                 250                 255

Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp
            260                 265                 270

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
        275                 280                 285

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
    290                 295                 300

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
305                 310                 315                 320

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
                325                 330                 335

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
            340                 345                 350

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
        355                 360                 365

Glu Tyr Asn Thr Ser Asn Pro Asp
    370                 375


<210> SEQ ID NO 138
<211> LENGTH: 366
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG1FcdeltaK-C-T2m fusion

<400> SEQUENCE: 138

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Pro Pro Cys Pro Ala Pro
1               5                   10                  15

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45
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```
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65                  70                  75                  80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

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

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220

Leu Ser Leu Ser Pro Gly Ile Pro Pro His Val Gln Lys Ser Val Asn
225                 230                 235                 240

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
                245                 250                 255

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
            260                 265                 270

Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
        275                 280                 285

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
    290                 295                 300

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
305                 310                 315                 320

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
                325                 330                 335

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
            340                 345                 350

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        355                 360                 365


<210> SEQ ID NO 139
<211> LENGTH: 374
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-(G3S)2-hIgG1FcdeltaK-C-T2m fusion

<400> SEQUENCE: 139

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Gly Gly Gly Ser Gly Gly
1               5                   10                  15

Gly Ser Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
            20                  25                  30

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
        35                  40                  45
```

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Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
    50                  55                  60

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
65                  70                  75                  80

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
                85                  90                  95

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
            100                 105                 110

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
        115                 120                 125

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
    130                 135                 140

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
145                 150                 155                 160

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
                165                 170                 175

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
            180                 185                 190

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
        195                 200                 205

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
    210                 215                 220

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro
225                 230                 235                 240

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
                245                 250                 255

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
            260                 265                 270

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
        275                 280                 285

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
    290                 295                 300

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
305                 310                 315                 320

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
                325                 330                 335

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
            340                 345                 350

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
        355                 360                 365

Asn Thr Ser Asn Pro Asp
    370


<210> SEQ ID NO 140
<211> LENGTH: 368
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG2FcdeltaK-CC-T2m fusion

<400> SEQUENCE: 140

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Val Glu Cys Pro Pro Cys
1               5                   10                  15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30
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```
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
        115                 120                 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    130                 135                 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
            180                 185                 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His Val Gln Lys Ser
225                 230                 235                 240

Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe
                245                 250                 255

Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn
            260                 265                 270

Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys
        275                 280                 285

Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile
    290                 295                 300

Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe
305                 310                 315                 320

Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys
                325                 330                 335

Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys
            340                 345                 350

Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        355                 360                 365


<210> SEQ ID NO 141
<211> LENGTH: 374
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG4FcdeltaK-CC-228P-T2m fusion

<400> SEQUENCE: 141

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Glu Ser Lys Tyr Gly Pro
1               5                   10                  15

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
            20                  25                  30
```

```
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
        35                  40                  45

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
    50                  55                  60

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
65                  70                  75                  80

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
                85                  90                  95

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
            100                 105                 110

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
        115                 120                 125

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
    130                 135                 140

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
145                 150                 155                 160

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
                165                 170                 175

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
            180                 185                 190

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
        195                 200                 205

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
    210                 215                 220

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Ile Pro
225                 230                 235                 240

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
                245                 250                 255

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
            260                 265                 270

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
        275                 280                 285

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
    290                 295                 300

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
305                 310                 315                 320

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
                325                 330                 335

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
            340                 345                 350

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
        355                 360                 365

Asn Thr Ser Asn Pro Asp
    370


<210> SEQ ID NO 142
<211> LENGTH: 374
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG4FcdeltaK-CC-228P-409K-T2m fusion

<400> SEQUENCE: 142

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Glu Ser Lys Tyr Gly Pro
1               5                   10                  15
```

```
Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
            20                  25                  30

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
        35                  40                  45

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
    50                  55                  60

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
65                  70                  75                  80

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
                85                  90                  95

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
            100                 105                 110

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
        115                 120                 125

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
    130                 135                 140

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
145                 150                 155                 160

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
                165                 170                 175

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
            180                 185                 190

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
        195                 200                 205

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
    210                 215                 220

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Ile Pro
225                 230                 235                 240

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
                245                 250                 255

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
            260                 265                 270

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
        275                 280                 285

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
    290                 295                 300

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
305                 310                 315                 320

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
                325                 330                 335

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
            340                 345                 350

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
        355                 360                 365

Asn Thr Ser Asn Pro Asp
    370
```

<210> SEQ ID NO 143
<211> LENGTH: 508
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG1FcdeltaK-CC-T22d35 fusion

<400> SEQUENCE: 143

```
Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Lys Thr His Thr Cys
1               5                   10                  15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
            20                  25                  30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
        35                  40                  45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
    50                  55                  60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65                  70                  75                  80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
                85                  90                  95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
            100                 105                 110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
        115                 120                 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
    130                 135                 140

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145                 150                 155                 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
                165                 170                 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
            180                 185                 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
        195                 200                 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
    210                 215                 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His
225                 230                 235                 240

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
                245                 250                 255

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
            260                 265                 270

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
        275                 280                 285

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
    290                 295                 300

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
305                 310                 315                 320

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
                325                 330                 335

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
            340                 345                 350

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
        355                 360                 365

Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
    370                 375                 380

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
385                 390                 395                 400

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
                405                 410                 415
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```
Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
            420                 425                 430

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
        435                 440                 445

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
    450                 455                 460

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
465                 470                 475                 480

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
                485                 490                 495

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            500                 505


<210> SEQ ID NO 144
<211> LENGTH: 504
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG2FcdeltaK-CC-T22d35 fusion

<400> SEQUENCE: 144

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Val Glu Cys Pro Pro Cys
1               5                   10                  15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
        115                 120                 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    130                 135                 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
            180                 185                 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His Val Gln Lys Ser
225                 230                 235                 240

Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe
                245                 250                 255

Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn
            260                 265                 270
```

```
Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys
        275                 280                 285

Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile
    290                 295                 300

Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe
305                 310                 315                 320

Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys
                325                 330                 335

Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys
            340                 345                 350

Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        355                 360                 365

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
    370                 375                 380

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

Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
                405                 410                 415

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
            420                 425                 430

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
        435                 440                 445

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
    450                 455                 460

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
465                 470                 475                 480

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
                485                 490                 495

Glu Tyr Asn Thr Ser Asn Pro Asp
            500


<210> SEQ ID NO 145
<211> LENGTH: 510
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG4FcdeltaK-CC-228P-T22d35 fusion

<400> SEQUENCE: 145

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Glu Ser Lys Tyr Gly Pro
1               5                   10                  15

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
            20                  25                  30

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
        35                  40                  45

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
    50                  55                  60

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
65                  70                  75                  80

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
                85                  90                  95

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
            100                 105                 110

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
        115                 120                 125
```

```
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
    130                 135                 140

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
145                 150                 155                 160

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
                165                 170                 175

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
            180                 185                 190

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
        195                 200                 205

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
    210                 215                 220

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Ile Pro
225                 230                 235                 240

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
                245                 250                 255

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
            260                 265                 270

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
        275                 280                 285

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
    290                 295                 300

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
305                 310                 315                 320

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
                325                 330                 335

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
            340                 345                 350

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
        355                 360                 365

Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn
    370                 375                 380

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
385                 390                 395                 400

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
                405                 410                 415

Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
            420                 425                 430

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
        435                 440                 445

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
    450                 455                 460

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
465                 470                 475                 480

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
                485                 490                 495

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            500                 505                 510
```

<210> SEQ ID NO 146
<211> LENGTH: 510
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG4FcdeltaK-CC-228P-409K-T22d35 fusion

<400> SEQUENCE: 146

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Glu Ser Lys Tyr Gly Pro
1 5 10 15

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
20 25 30

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
35 40 45

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
50 55 60

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
65 70 75 80

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
85 90 95

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
100 105 110

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
115 120 125

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
130 135 140

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
145 150 155 160

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
165 170 175

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
180 185 190

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
195 200 205

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
210 215 220

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Ile Pro
225 230 235 240

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
245 250 255

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
260 265 270

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
275 280 285

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
290 295 300

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
305 310 315 320

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
325 330 335

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
340 345 350

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
355 360 365

Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn
370 375 380

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
385 390 395 400

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys

```
                405                 410                 415

Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
            420                 425                 430

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
        435                 440                 445

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
    450                 455                 460

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
465                 470                 475                 480

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
                485                 490                 495

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
            500                 505                 510


<210> SEQ ID NO 147
<211> LENGTH: 644
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG1FcdeltaK-CC-T2-T2-T2 fusion

<400> SEQUENCE: 147

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Lys Thr His Thr Cys
1               5                   10                  15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
            20                  25                  30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
        35                  40                  45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
    50                  55                  60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65                  70                  75                  80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
                85                  90                  95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
            100                 105                 110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
        115                 120                 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
    130                 135                 140

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145                 150                 155                 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
                165                 170                 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
            180                 185                 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
        195                 200                 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
    210                 215                 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His
225                 230                 235                 240

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
                245                 250                 255

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
```

```
            260                 265                 270

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
        275                 280                 285

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
    290                 295                 300

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
305                 310                 315                 320

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
                325                 330                 335

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
            340                 345                 350

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
        355                 360                 365

Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp
    370                 375                 380

Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys
385                 390                 395                 400

Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys
                405                 410                 415

Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val
            420                 425                 430

Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr
        435                 440                 445

Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp
    450                 455                 460

Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu
465                 470                 475                 480

Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile
                485                 490                 495

Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His
            500                 505                 510

Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly
        515                 520                 525

Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser
    530                 535                 540

Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser
545                 550                 555                 560

Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn
                565                 570                 575

Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro
            580                 585                 590

Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met
        595                 600                 605

Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser
    610                 615                 620

Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr
625                 630                 635                 640

Ser Asn Pro Asp


<210> SEQ ID NO 148
<211> LENGTH: 640
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
```

<223> OTHER INFORMATION: D10-hIgG2FcdeltaK-CC-T2-T2-T2 fusion

<400> SEQUENCE: 148

```
Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Val Glu Cys Pro Pro Cys
1               5                   10                  15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
        115                 120                 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    130                 135                 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
            180                 185                 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Ile Pro Pro His Val Gln Lys Ser
225                 230                 235                 240

Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe
                245                 250                 255

Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn
            260                 265                 270

Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys
        275                 280                 285

Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile
    290                 295                 300

Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe
305                 310                 315                 320

Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys
                325                 330                 335

Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys
            340                 345                 350

Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
        355                 360                 365

Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr
    370                 375                 380

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

```
Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys
                405                 410                 415

Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val
            420                 425                 430

Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp
        435                 440                 445

Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro
    450                 455                 460

Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met
465                 470                 475                 480

Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu
                485                 490                 495

Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser
            500                 505                 510

Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe
        515                 520                 525

Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn
    530                 535                 540

Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys
545                 550                 555                 560

Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile
                565                 570                 575

Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe
            580                 585                 590

Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys
        595                 600                 605

Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys
    610                 615                 620

Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp
625                 630                 635                 640


<210> SEQ ID NO 149
<211> LENGTH: 646
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG4FcdeltaK-CC-228P-T2-T2-T2 fusion

<400> SEQUENCE: 149

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Glu Ser Lys Tyr Gly Pro
1               5                   10                  15

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
            20                  25                  30

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
        35                  40                  45

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
    50                  55                  60

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
65                  70                  75                  80

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
                85                  90                  95

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
            100                 105                 110

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
        115                 120                 125
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Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
    130                 135                 140

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
145                 150                 155                 160

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
                165                 170                 175

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
            180                 185                 190

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
        195                 200                 205

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
    210                 215                 220

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Ile Pro
225                 230                 235                 240

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
                245                 250                 255

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
            260                 265                 270

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
        275                 280                 285

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
    290                 295                 300

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
305                 310                 315                 320

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
                325                 330                 335

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
            340                 345                 350

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
        355                 360                 365

Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys Ser Val Asn
    370                 375                 380

Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln
385                 390                 395                 400

Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys
                405                 410                 415

Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln
            420                 425                 430

Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu
        435                 440                 445

Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu
    450                 455                 460

Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro
465                 470                 475                 480

Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp
                485                 490                 495

Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro
            500                 505                 510

Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn
        515                 520                 525

Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg
    530                 535                 540

Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile
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545                 550                 555                 560

Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg
                565                 570                 575

Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys
            580                 585                 590

Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys
        595                 600                 605

Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser
    610                 615                 620

Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr
625                 630                 635                 640

Asn Thr Ser Asn Pro Asp
                645


<210> SEQ ID NO 150
<211> LENGTH: 649
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: D10-hIgG4FcdeltaK-CC-228P-409K-T2-T2-T2 fusion

<400> SEQUENCE: 150

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Glu Ser Lys Tyr Gly Pro
1               5                   10                  15

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
            20                  25                  30

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
        35                  40                  45

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
    50                  55                  60

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
65                  70                  75                  80

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
                85                  90                  95

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
            100                 105                 110

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Ser Glu Gln Glu
        115                 120                 125

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    130                 135                 140

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
145                 150                 155                 160

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

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
            180                 185                 190

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        195                 200                 205

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
    210                 215                 220

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
225                 230                 235                 240

Gly Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val
                245                 250                 255

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
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            260                 265                 270

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
        275                 280                 285

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
    290                 295                 300

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
305                 310                 315                 320

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
                325                 330                 335

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
            340                 345                 350

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
        355                 360                 365

Glu Glu Tyr Asn Thr Ser Asn Pro Asp Ile Pro Pro His Val Gln Lys
    370                 375                 380

Ser Val Asn Asn Asp Met Ile Val Thr Asp Asn Asn Gly Ala Val Lys
385                 390                 395                 400

Phe Pro Gln Leu Cys Lys Phe Cys Asp Val Arg Phe Ser Thr Cys Asp
                405                 410                 415

Asn Gln Lys Ser Cys Met Ser Asn Cys Ser Ile Thr Ser Ile Cys Glu
            420                 425                 430

Lys Pro Gln Glu Val Cys Val Ala Val Trp Arg Lys Asn Asp Glu Asn
        435                 440                 445

Ile Thr Leu Glu Thr Val Cys His Asp Pro Lys Leu Pro Tyr His Asp
    450                 455                 460

Phe Ile Leu Glu Asp Ala Ala Ser Pro Lys Cys Ile Met Lys Glu Lys
465                 470                 475                 480

Lys Lys Pro Gly Glu Thr Phe Phe Met Cys Ser Cys Ser Ser Asp Glu
                485                 490                 495

Cys Asn Asp Asn Ile Ile Phe Ser Glu Glu Tyr Asn Thr Ser Asn Pro
            500                 505                 510

Asp Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met Ile Val
        515                 520                 525

Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys Phe Cys
    530                 535                 540

Asp Val Arg Phe Ser Thr Cys Asp Asn Gln Lys Ser Cys Met Ser Asn
545                 550                 555                 560

Cys Ser Ile Thr Ser Ile Cys Glu Lys Pro Gln Glu Val Cys Val Ala
                565                 570                 575

Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val Cys His
            580                 585                 590

Asp Pro Lys Leu Pro Tyr His Asp Phe Ile Leu Glu Asp Ala Ala Ser
        595                 600                 605

Pro Lys Cys Ile Met Lys Glu Lys Lys Lys Pro Gly Glu Thr Phe Phe
    610                 615                 620

Met Cys Ser Cys Ser Ser Asp Glu Cys Asn Asp Asn Ile Ile Phe Ser
625                 630                 635                 640

Glu Glu Tyr Asn Thr Ser Asn Pro Asp
                645
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The invention claimed is:

1. A polypeptide construct comprising:

a first portion comprising the second constant domain (CH2) and/or third constant domain (CH3) of an antibody heavy chain, and

a second portion comprising at least two TGF-β superfamily receptor ectodomains (TβSR-ED) linked in tandem,

wherein the N-terminus of the second portion is linked to the C-terminus of the first portion,

wherein the at least two TβSR-EDs are TGF-β receptor II ectodomains (TβR-II-EDs), and

wherein the polypeptide construct has neutralization activity against TGF-β2.

2. The polypeptide construct of claim 1, wherein the second portion comprises two TβSR-ED.

3. The polypeptide construct of claim 1, wherein the first portion further comprises a CH1, a CH1 and VH, or CH1 and scFv.

4. The polypeptide construct of claim 1, wherein the polypeptide construct shows longer in vivo half-life compared to the half-life of the second portion alone.

5. The polypeptide construct of claim 1, wherein the polypeptide construct forms a dimeric polypeptide.

6. The polypeptide construct of claim 1, wherein the construct comprises an antibody or an antigen binding fragment thereof, or a targeting moiety.

7. The polypeptide construct of claim 6, wherein the antibody or the antigen binding fragment thereof binds to an antigen that is not PD-L1, CD4, CD6, CD20, CD25, MUC-1, IL-2, IL-6, or CTLA-4.

8. The polypeptide construct according to claim 6, wherein the targeting moiety comprises a poly-aspartate sequence motif for bone targeting.

9. A composition comprising one or more than one independently selected polypeptide construct of claim 1 and a pharmaceutically-acceptable carrier, diluent, or excipient.

10. The polypeptide construct of claim 1, wherein the N-terminus of the second portion is directly linked to the C-terminus of the first portion, and wherein the C-terminal residue of the amino acid sequence of the first portion is not a lysine residue.

11. The polypeptide construct of claim 1, wherein each of the at least two TβSR-EDs comprises the amino acid sequence set forth in SEQ ID NO: 35.

12. The polypeptide construct of claim 11, wherein the at least two TβSR-EDs are joined by a linker.

13. The polypeptide construct of claim 12, wherein the linker comprises the amino acid sequence set forth in SEQ ID NO: 39.

14. The polypeptide construct of claim 1, wherein the second portion comprises the amino acid sequence set forth in SEQ ID NO: 46.

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