(19) (KR)
(12) (A)

(11) 10-2010-0041849
(43) 2010 04 22

(51) Int. Cl.

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C07K 16/28 (2006.01) *A61P 37/06* (2006.01)

(21) 10-2010-7003921
(22) ( ) 2008 07 25

(85) 2010 02 23
(86) PCT/US2008/009037
(87) WO 2009/014745
2009 01 29

(30)
60/962,022 2007 07 25 (US)

: 39

(71)
,
, 06410, ,
352

(72)
, .
, 73151, ,
10325
,
, 06371, ,
14

(74)

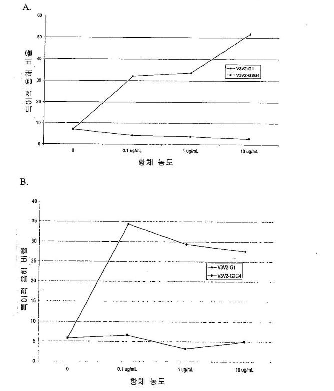
(54) 200

(57)

CD200 CD200R .
, CD200 CD200R
.

\- 6

T-세포 수용체 신호전달을 통하여 활성화된 인간 T 세포는 항-CD200 매개된 ADCC에 대한 감수성 표적으로서 기능한다.



1

, i) CD200 CD200R
ii)
.

2

1 , .

3

2 , .

4

2 , .

5

2 , .

6

1 , -CD200 -
.

7

1 , CD200R - (nonagonistic) CD200
.

8

1 , A
.

9

3 , -CD200 - - ,
- , - , -
, - , - -
.

10

3 , - - , Fab, Fab', $F(ab')_2$, $F(ab')_3$, Fd, Fv, ,
CD200 -CD200
.

11

1 ,
.

12

11 , A
.

13

1 , (adriamycin), (azathioprine), (busulfan), (cyclophosphamide), (cyclosporine) A, (fludarabine), 5- (fluorouracil), (methotrexate), (mycophenolate mofetil), - , (sirolimus)(rapamycin), (tacrolimus)(FK-506) .

14

1 , (muromonab)-CD3, (alemtuzumab), (basiliximab), (daclizumab), (rituximab), - (thymocyte globulin) .

15

1 , .

16

15 , , ,
.

17

16 , ,
.

18

16 ,
.

19

1 , i) , ii) , iii)
.

20

16 , (rejection episode)
.

21

17 , ,
.

22

16 , , , , - , , , , (solid organ) .

23

1 , - .

24

17 , , -
.

25

17 , , -
.

26

16 , ,
:

(a) 6 ;

(b) 1 ;

(c) 5 .

27

26 , (accommodation) .

28

1 ,
.

29

28 , (autoimmune hemolytic anemia)
.

30

1 , .

31

1 , .

32

1 , .

33

1 , .

34

,
i) ii) CD200 CD200R
,
(immunosuppression) (immunomodulation)
.

35

34 , , .

36

34 , .

37

34 , A .

38

,
CD200 CD200R
, .

39

38 , -CD200 -
.

[0001]

[0002] 2007 7 25 U.S. No. 60/962,022 ,
.

[0003]

[0004] OX-2/CD200(, CD200) .
.
(tolerance) CD200- , , -CD200
.

[0005]

[0006] (infectious agent) .
, , , , , ,
. (, ,) ,
. , ,
, (life-saving procedure) . (chronic organ failure) . (,
) , ( )
. 1 (surviving rate) ,
88.3%, 94.4% .
5 63.3% 76.5% (the Organ Procurement and Transplantation Network (OPTN)
the Scientific Registry of Transplant Recipients (SRTR) OPTN/SRTR Annual Report, 2002. Chapter 1. http//.). , 1
, 80.2% 76.5% . 5 63.5% 73.0%
(the Organ Procurement and Transplantation Network (OPTN) the Scientific Registry of Transplant Recipients (SRTR) OPTN/SRTR Annual Report, 2002. Chapter 1. http//.). , A ,
. . ,
, .

[0007] . (autologous graft) (autograft) . 2 (syngeneic) (syngeneic graft) . 2 (allogenic graft) (allograft) , (xenogenic graft) (xenograft) .

[0008] , 40,000 , , , (Abbas et al., 2000; Cellular and Molecular Immunology (4th edition), p. 363-383 (W. B. Saunders Company, New York).

, , , , , , , , , , , , (islet), , , (hematopoietic cell) . , . , . , .

[0009] , , (genetic background) , (,), (histocompatibility antigen), , HLA (major histocompatibility complex, MHC) . , , . . (1) ; (2) (*de novo*); (3) . , T- / , , , , . (alloantigen) , (xenoantigen) . , (alloreactive) (xenoreactive) .

[0010] (cellular immunity)(T (immunocompetent cell)) (humoral immunity)( ) (: Rocha et al. 2003 Immunol. Rev. 196: 51-64). T , . , CD8+ T / (, -) MHC . I II , MHC CD8+ CD4+ T . MHC CD4+/T , T , 1(IL-I) . T IL-2 , T (lymphokine)- (killer cell) , IL-4 IL-6 . , IL-2 (interferon gamma), (tumor necrosis factor) (proinflammatory cytokine) .

[0011] APC(- , ,) , . APC . APC (circulation) (lymph node) , T . APC , T .

[0012] B- , - (,) . , B- , , CD4+ T . (endothelial cell) MHC (coagulation) , . , Fc - (ADCC) . , , , HLA I II .

[0013] , , . , (fever),
(leukocytosis) (fatigue) (systemic symptom)
(swelling) (tenderness) . .

[0014] .
(cyclosporine)(CsA); (tacrolimus)(FK-506);
(azathioprine)(AZ); (mycophenolate mofetil)(MMF); (mizoribine)(MZ);
(leflunomide)(LEF); (adrenocortical steroid)(,
(adrenocortical hormone), (corticosteroid), (corticoid)), ,
(prednisolone) (methylprednisolone); (sirolimus)(,);
(deoxyspergualin)(DSG); FTY720(, Fingolimod, : 2- -2-[2-(4-
)]-1,3-) . , T
(costimulatory signal transduction molecule) CTLA-4 CD28
; CTLA-4
CTLA-4 .

[0015] , ,
. (autoimmunity)
, .

[0016] OX-2, CD200 . CD200
B , T , ,
(immunoglobulin gene family) (homology) . CD200 ,
CD200- Th1 (Gorczynski et al.,
1998 Transplantation 65: 1106-1114). , CD200 -
(sheep erythrocyte) (Gorczynski
et al. 1999 J. Immunol. 163: 1654-1660). , CD200- (knockout)
APC - , (central nervous system) ,
, (susceptibility) (Hoek et
al. 2000 Science 290: 1768-1771). CD200 / (lineage) T-
CD200R CD200 (Hoek et al. supra;
Gorczynski et al. 2000 J. Immunol. 165: 4854).

[0017] CD200 , CD200
. , -CD200 (-CD200 F(ab')$_2$)
CD200Fc- (Gorczynski et al. 2002 Transplantation. 73: 1948-53).

[0018] , -CD200 -CD200
.
.

[0019]

[0020] -CD200 (immunological challenge), ,
. ,
, , ,
(,). ,
, , , (rejection episode)
. CD200 , CD200
(, , ,
) .

[0021] , CD200 . CD200- ,
, , , , - , (prodrug) /
. CD200 CD200 (CD200R)
, .

[0022] , CD200 -CD200 . ,
, (, , CDR- , , ,
- ,),
. , (, ,
), , , , , (primatized) .
, - , , Fab, Fab', F(ab')$_2$, F(ab')$_3$, Fd, Fv, (dAb),
(monovalent) (divalent) , (CDR) , - (, scFv, scFab,
scFabΔC), (diabody), (triabody), (minibody), (nanobody), CD200
, ;
. , , , - -CD200 ,
- . , IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgA,
IgD / IgE (framework) .

[0023] , CD200 CD200 CD200R
. , CD200 CD200R -CD200
- . , - ,
, - .
, CD200R - (non-agonistic) CD200 .

[0024] , , i)
CD200 CD200R ii)
. , . ,
. , . ,
, . , -CD200
- . , CD200R -
CD200 . , T , B , T B ,
. , A .

[0025] , ,
-CD200 - . ,
-CD200 - - , -
, - , - ,
- , - - . -
, - , Fab, Fab', F(ab')$_2$, F(ab')$_3$, Fd, Fv, , CD200
-CD200 .
- , , .
, ( ) (PEG) .

[0026] , : a) APC
; b) (CD4+) T ; c) (CD4+) T- ; d) B ; e) B
; f) B- . , B-
, IgG, IgM, IgG1, IgG2a .

[0027] , ,
-CD200 - ,
. T , B , T B
, . ,
. , A .

[0028] , -CD200
(adriamycin), (azathioprine), (busulfan), (cyclophosphamide),
(cyclosporine) A, (cytoxan), (fludarabine), 5- (fluorouracil),
(methotrexate), (mycophenolate mofetil), 6-
(mercaptopurine), (corticosteroid), - ,
(sirolimus)(rapamycin), (tacrolimus) . ,
(muromonab)-CD3, (alemtuzumab), (basiliximab),
(daclizumab), (rituximab), - (thymocyte globulin) IVIg
. , (complement pathway)
(, (, -C5)).

[0029] , ,
. , , .

[0030] , B ,
(a) -CD200 - (b)
. , CD200- T
, (a) -CD200 - (b)
. , B
, (a) -CD200 - (b)
. , -CD200 -
. ,
, , . , ,
, .

[0031] , , (a)
-CD200 - (b)
. , a) -CD200 b)
. , -CD200 -
- , - , -
, - , - , -
- . - , - , Fab,
Fab', F(ab')$_2$, F(ab')$_3$, Fd, Fv, , CD200 -CD200
. - ,
, . , ( ) (PEG)
.

[0032] , -CD200 -
. , .
, . ,
, . , ,
.

[0033] , , ,
, - , , , ,
(solid organ) . , ,
, , , , , , , , , , , , , ,
, (hematopoietic cell) .

[0034] , T B , T
B . , (complement pathway)
/ - . ,
. , A
.

[0035] , (adriamycin),
(azathioprine), (busulfan), (cyclophosphamide),
(cyclosporine) A, (fludarabine), 5- (fluorouracil),
(methotrexate), (mycophenolate mofetil), 6- (mercaptopurine),
(corticosteroid), - , (sirolimus)(rapamycin),
(tacrolimus)(FK-506) . ,
(muromonab)-CD3, (alemtuzumab), (basiliximab), (daclizumab),
(rituximab), - (thymocyte globulin) IVIg .

[0036] , -CD200
. , , -
. - IgG, IgM, IgG1, IgG2a .
, , - ,
. , , -
, .

[0037] , -CD200
. , , CD4+
CD8+ T . , , -
, . ,
, - ,
.

[0038] , ,
(a) -CD200 - (b)
. ,
, (a) -CD200 - (b)
. -CD200 -
- , - ,
- , - , - ,
- - . - , -
, Fab, Fab', F(ab')$_2$, F(ab')$_3$, Fd, Fv, , CD200 -CD200
.

[0039] ,
, 15%, 20%, 25%,
30%, 40%, 50% . ,
, (monotherapy) .

[0040] , ,
6 , 1 ; 5 ; 7.5 ;
10 . ,
(accommodation) .

[0041] , , , -
. , .

[0042] , -CD200 -
. , -
.

[0043] -CD200 - , -
CD200 - . ,
.

[0044] .

.

[0045]

[0046] **I.**

[0047] *A.*

[0048] (hyperacute rejection) . (vasculature) (hemorrhage) (thrombotic occlusion) . (endothelium) (complement) , , (intravascular thrombosis) (vascular occlusion) , (irreversible ischemic damage) (Abbas et al., 2000 Cellular and Molecular Immunology (4th edition), p. 363-383 (W. B. Saunders Company, New York)). , IgM , , ABO . (natural antibody) . IgM , , ABO . ABO , , , MHC , IgG . IgG , (blood transfusion), , (multiple pregnancy) .

[0049] T , (parenchymal) , (Abbas et al., supra). T MHC . T , (necrosis) . CD4$^+$ CD8$^+$ T . CD8$^+$ T . CD4$^+$ T (delayed-type hypersensitivity)- ; CD4$^+$ T (Abbas et al., supra). , , (Abbas et al., supra).

[0050] (fibrosis) . (pathogenesis) . (intimal smooth muscle) (Abbas et al., supra). (arteriosclerosis) 6 1 .

[0051] , T . CD4$^+$ T . (major histocompatibility complex, MHC) , I II MHC . I MHC HLA-A, HLA-B HLA-C . II MHC HLA-DR, HLA-DQ HLA-DP . , I MHC H-2K, H-2D H-2L , II MHC I-A I-E . CD4$^+$ T MHC , (clonal proliferation) . T / , B CD8$^+$ T . / , B - , CD8$^+$ T (apoptosis) (cell lysis) - .

[0052] , - HLA , . , (important factor) . , , I II -HLA (, " -MHC ") . , - . - , Rifle et al., Transplantation, 2005 79:S14-S18 .

[0053] *B.*

[0054] , . , . , , T- , , . (prescreening) , . -HLA (immunoadsorption) . , -T , , OKT3, - (anti-Thymocyte Globulin, ATG), (cyclosporine) A, (tacrolimus)(FK 506) . , (glucocorticoid) / (azathioprine)( ) . ATG ALG, OKT3, (daclizumab), (basiliximab), (corticosteroid), 15- (deoxyspergualin), LF15-0195, (cyclosporin), (tacrolimus), (purine analog), , (azathioprine), (methotrexate), (mycophenolate mofetil), 6- (mercaptopurine), (bredinin), (brequinar), (leflunomide), (cyclophosphamide), (sirolimus), -CD4 , CTLA4-Ig, (rituxan), -CD154 , -LFA1 , -LFA-3 , -CD2 , -CD45 .

[0055] (,) . Stepkowski (2000). Exp. Rev. Mol. Med. 21 June, world wide web at expertreviews.org/00001769h.htm .

[0056] A . -2 IL-2 (-2 mRNA). , T . NFAT(T) (dephosphorylation) , NFAT -2 . , A $CD4^+$ T . -2 .

[0057] (Sirolimus), SDZ RAD, -2 -2 , .

[0058] (purine) (pyrimidine) (biosynthesis) . DNA , T (cell division) . , T T . (azathioprine), (methotrexate), (mycophenolate mofetil, MMF) (mizoribine)(bredinin) . (brequinar sodium) (leflunomide) . (cyclophosphamide) .

[0059] T T . OKT3 T
CD3 . , T T
, T .

[0060]
. , T . T , HLA
(partial mismatch) . CD40
-CD40 ( ) / CD28-B7 (U.S.
Patent 6,280,957). PCT WO 01/37860 Th1 -CD3
IL-5 . PCT WO 00/27421 (tumor necrosis
factor)-α . Glotz et
al., 2002 Am. J. Transplant. 2:758-760 (IVIg) -HLA
, HLA-
. (plasma exchange)(Taube et al., 1984 Lancet 1 :824-828),
(Hiesse et al., 1992 Nephrol. Dial. Transplant. 7:944-951),
(Montgomery et al., 2000 Transplantation 70:887-895) . Changelian et al., 2003 Science
302:875-878 (γc) (-2, -4, -7, -9,
-15, -21) (Janus kinase) 3(JAK3)
, T . ICAM-I
, - (leukocyte-function associated) 1(LFA-1)
(Stepkowski, supra). , -ICAM-I
-LFA-1 (Stepkowski, supra). ,
,
(Stepkowski, supra). , ,
TGF-β (U.S. Patent Application
Publication US 2003/0180301).

[0061] *C. CD200*

[0062] CD200 . CD200
(, T- , B- (Barclay et al., 2002 TRENDS Immunol. 23:285-290)),
I (transmembrane
glycoprotein) . (myeloid cell) T - CD200R
(Wright et al. 2003 J. Immunol. 171: 3034-3046; Wright et al., 2000 Immunity 13:233-242);
CD200:CD200R - (immune
tolerance) (Rosenblum et al. 2004 Blood 103: 2691-2698).

[0063] , Gorczynski CD200 . ,
Gorczynski et al., Clin. Immunol. 104:256-264 (2002) - (collagen-induced
arthritis, CIA) , CD200(CD200Fc) CIA .
(transplant setting) , Gorczynski et al., Eur. J. Immunol. 31: 2331-2337 (2001) CD200
, -CD200
.

[0064] , -CD200 .
, T- (inactivation)
/ B- (,) . , CD200
(resting cell) T B .
-CD200 T B -
(antibody-mediated cell cytotoxicity(ADCC), - (complement-dependent cytotoxicity,
CDC) / , , . ,
. ,
, .
, B / T ,

. ,
, CD200 CD200 (CD200R)
. ,
, CD200R CD200 .

[0065] -CD200 : (i)
(, B B); (ii) , T
(, T) (, TNF-α IL-12) ; (iii)
(IVIg) (, CD200 -CD200
); (iv) (anergy) ; (v)
; / (vi) CD200 .
, CD200 (, 5 ,
2), (,
vs. (adapter protein), , DAP12) (Wright et al. J. Immunol., 2003, 171: 3034-3046). CD200R
. , CD200 CD200:CD200R
, -CD200 CD200 (cross linking) , .

[0066] **II. CD200-**

[0067] .
, CD200- . , CD200- CD200
. CD200- , , ,
. , CD200- CD200 CD200R
. , CD200- CD200- .

[0068] , CD200- .
. , .
, .
, -CD200 .

[0069] , CD200- -CD200 . , " " CD200
. , (,
, CDR- , , ,),
- , (, ,
, , - . , , ,
, , (primatized) . - , Fab, Fab', F(ab')$_2$,
F(ab')$_3$, Fd, Fv, (dAb), (monovalent) (divalent) , (CDR)
, - (, scFv, scFab, scFabΔC), (diabody), (triabody),
(minibody), (nanobody), CD200 ,
; . Fd V_H C_{H1}
; Fv (single arm) V_L V_H ; scFv
(peptide linker) (V_H) (V_L) ;
scFab Fd(fragment difficult) ;
scFabΔC (cysteine) scFab (, Hust et al., BMC Biotech 7: 14 (2007)
) , dAb ( ) (, V_H V_L)(Ward et al., Nature 341 :544-546 (1989)) . , Holliger and Hudson, Nature Biotechnology 23: 1126-1136 (2005)
. , , Fv scFv ,
. (*in vivo* stability) (*in vivo* half-life) , , ( ) (

) .

[0070] , Fc ; Fc . Fc , , ADCC CDC . Fc , CD200 ; -CD200 .

[0071] , / -CD200 . " (homology)" " (identity)" " (similarity)" 2 2 . , . , ; (, /) , ( ) . / . " " (motif) , . , " " (sequence matching) , , (gap) 2 . (largest match) (: Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part I,Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; Carillo, H., and Lipman, D., SIAM J. Applied Math., 48: 1073 1988, Devereux, J., et al., Nucleic Acids Research 12(1): 387 (1984), BLASTP, BLASTN, FASTA (Altschul, S. F. et al., J. Molec. Biol. 215: 403-410 (1990); Altschul et al. Nuc. Acids Res. 25: 3389-3402 (1997)), BLAST X (BLAST Manual, Altschul, S., et al., NCBI NLM NIH Bethesda, Md. 20894; Altschul, S., et al., J. Mol. Biol. 215: 403-410 (1990)). " " " - " 40% , , 25% . , ( ) / .

[0072] . . , .

[0073] . , -CD200 (immunogen) CD200 , CD200 , CD200 , - , . , . , CDR- , , CD200 .

[0074] , (" ") (target specificity) (bait) , CD200- , . - -CD200 .

[0075] - DNA . (immunogenicity) . , CDR (grafting) , (framework modification) (: U.S. Patent No. 5,225,539).

[0076] , ,
. DNA , ,
. ,
.

[0077] , , ,
(*E. coli*) . ,
DNA , DNA
. , . ,

, DNA .

[0078] ,
(,), (,
, , , 2- , , , ,
) (, DMEM(Dulbecco's Modified Eagle Medium) RPMI 1640) .
. , LE, NZCYM, NZYM, NZM, Terrific Broth, SOB, SOC, 2 x YT, M9 . YPD, YEPD, ,
(Complete Minimal Dropout Medium) .

[0079] ,
(scale-up) . , , , ,
(,),
(, , ,) .

[0080] . ,
- .
, , , , (pristane)(-)
. 1 3 , . ,
Balb/c - ,
Sp2/0
- Balb/c . 1 2 , .

[0081] , Kohler and Milstein,(1975) Nature 256:495-497; U.S. Patent No. 4,376, 110; Harlow and Lane, Antibodies: a Laboratory Manual,(1988) Cold Spring Harbor .
, W097/08320; U.S. Patent No. 5,427,908; U.S. Patent No. 5,508,717; Smith, 1985, Science, Vol.225, pp 1315-1317; Parmley and Smith 1988, Gene 73, pp 305-318; De La Cruz et al, 1988, Journal of Biological Chemistry, 263 pp 4318-4322; U.S. Patent No. 5,403,484; U.S. Patent No. 5223409; W088/06630; WO92/15679; U.S. Patent No. 5780279; U.S. Patent No. 5571698; U.S. Patent No. 6040136; Davis et al., Cancer Metastasis Rev.,1999;18(4):421-5; Taylor, et al., Nucleic Acids Research 20(1992): 6287-6295; Tomizuka et al.,Proc. Nat. Academy of Sciences USA 97(2)(2000): 722-727 . .

[0082] CD200- , , , ,
- , .

[0083] , , ,
, . ,
, , , - , DEAE-
/ (-) , , CD200-
, -A -G .

[0084] , CD200
. , CD200- , CD200

(pooled sample) . (
,) (panning) .

[0085] .
, ,
(ascite) - (deep-frozen) .

[0086] , CD200 .
, , , Balb/c CD200 ,
CD200- , CD200- ,
. -
, .
, . , CD200-
(CLL) Balb/c PAI Sp2/0-Ag 14
. ,
.

[0087] , , 2 4 , , 4 6 , CD200- 10^6 10^7
/ Balb/c ,
. 2 4 ,
, , PAI .
, 4000 30% 50% ,
3- 20- . ,
,
, , HAT .

[0088] " (chimeric)" . - 2
(,) .
(splicing) (: U.S. patent No. 4,816,567). , - .

[0089] - (,) " " . CDR- mAb
,
, . , -
. - , " (import)"
, , " " .
. , , Winter (Jones et al., Nature 321: 522-525 (1986); Reichmann et al., Nature, 332:323-327 (1988); Verheoeyen et al., Science, 239: 1534-1536 (1988))
, CDR CDR . ,
Staelens et al. 2006 Mol. Immunol 43: 1243-1257 . , - (,)
(CDR) - ( ), , , , ,
(specificity), (affinity) (binding capacity) -
( ) . ,
- (, " (back mutation)"). ,
(phage display library)
. . ,
, , ,
.

[0090] . " "
( ) .
(, ,
) . , " "

, , CDR (,)
. ((V), (D), (J)
(C)) (transgenic) , . ,
, (repertoire)
(,) (: Jakobovits et al., PNAS, 90:2551 (1993); Jakobovits et al., Nature, 362:255-258 (1993); Bruggermann et al., Year in Immuno., 7:33 (1993); Duchosal et al. Nature 355:258 (1992).
. ,
(rearrangement)
. RNA
(, CD200, , CD200) . ,
(display vector) . ,
, ,
, .
(display package)
. , (phage coat protein) . ,
(screening) .

[0091] , - (Hoogenboom et al., J. Mol. Biol, 227:381 (1991); Marks et al., J. Mol. Biol., 222:581-597 (1991); Vaughan et al. Nature Biotech 14:309 (1996)). V- .
, V- (:
US 6,794,132, 6,680,209, 4,634,666; Ostberg et al. (1983), Hybridoma 2:361-367).

[0092] , Mendez et al. Nature Genetics 15:146-156 (1997) Green and Jakobovits J. Exp. Med. 188:483-495 (1998) , . U.S.
5,939,598 6,673,986 . , 1995 6 5 U.S. 6,114,598, 6,075,181 6,162,963 . , 1996 10 2 U.S. 6,150,584; US 6,713,610 6,657,103, U.S. 10/421,011(US 2003-0229905 A1), 10/455,013(US 2004-0010810 A1), 10/627,250(US 2004-0093622 A1), 10/656,623(US 2006-0040363 A1), 10/658,521(US 2005-0054055 A1), 10/917,703(US 2005-0076395 A1) 10/978,297(US 2005-0287630 A1) . , 1993 7 23 PCT/US93/06926, 1996 6 12 No. EP 0 463 151 B1, 1994 2 3
No., WO 94/02602, 1996 10 31 No. WO 96/34096
1998 6 11 WO 98/24893 . ,
.

[0093] , GenPharm International, Inc. " (minilocus)" .
, Ig Ig ( ) .
V_H , D_H , J_H , mu (
,) (construct) . U.S. Pat. No. 5,545,807(Surani et al.); U.S. Pat. No. 5,545,806, 5,625,825, 5,625,126, 5,633,425, 5,661,016, 5,770,429, 5,789,650 5,814,318(, Lonberg and Kay); U.S. Pat. No. 5,591,669(Krimpenfort and Berns); U.S. Pat. No. 5,612,205, 5,721,367, 5,789,215(Berns et al.); U.S. Pat. No. 5,643,763(Choi and Dunn); GenPharm International . , U.S. 5,569,825, 5,877,397, 6,300,129, 5,874,299, 6,255,458 7,041,871 , . , No. 0 546 073 B1 No. WO 92/03918, WO 92/22645, WO 92/22647, WO 92/22670, WO 93/12227, WO 94/00569, WO 94/25585, WO 96/14436, WO 97/13852 WO 98/24884 ,
. , Taylor et al. (1992 Nuc. Acids. Res., 20:6287), Chen et al. (1993 Int. Immunol. 5: 647), Tuaillon et al. (1993 PNAS U S A. 90: 3720-4), Choi et al., (1993 Nature Genetics 4: 117), Lonberg et al. (1994 Nature 368: 856-859), Taylor et al. (1994 International Immunology 6: 579-591), Tuaillon et al. (1995 J Immunol. 154: 6453-65), Fishwild et al. (1996 Nature Biotechnology 14: 845),

Tuaillon et al. (2000 Eur J Immunol. 10: 2998-3005) , .

[0094] , - -CD200 - . - - - . (de-immunization) - (: PCT No. WO 04/108158 WO 00/34317). , - - T / B , , - T / B . - , , , - . T / B , , (: PCT Publication No. WO 02/069232), *in vitro* *in silico* , (, MHC , - T :MHC , - MHC , -) . , - -CD200 - - , Fab, Fv, scFv, Fab' F(ab')$_2$, , , (, , , CDR- , ,), - .

[0095] , CD200 CD200- / (insert) DNA . DNA DNA, DNA DNA DNA, ( ) DNA .

[0096] , CD200 CD200- / DNA / DNA , DNA . DNA , , / DNA . , / CDR . DNA (codon) (silent mutant) . (degenerate) . , (genetic code) . (restriction site) / , , (*E. coli*) , / .

[0097] , DNA DNA .

[0098] 4 (assembly) , DNA DNA , , .

[0099] IgG, , γ1, γ2, γ3 γ4; , γ1 γ4 CD200 CD200- DNA . κ λ, , κ DNA .

[0100] DNA , (spacer) , / / / /

DNA . DNA
DNA . , ,
. DNA DNA
, , .

[0101] - , ,
(detectable label) - . ,
- , , , , , , ,
, , , , , (, ,
RNAi, -), (, NMR X- (contrasting agent),
) . , -CD200 - (, Fab, Fv, -
scFv, Fab' F(ab')$_2$) - .
-CD200 - ,
, , PEG .

[0102] .
. DNA
(*E. coli*) gpt(Mulligan, R. C. and Berg, P., Proc. Natl. Acad. Sci., USA, 78: 2072 (1981))
Tn5 neo(Southern, P. J. and Berg, P., J. Mol. Appl. Genet., 1: 327 (1982))
(drug resistance gene) . DNA
, - (co-transfection) (Wigler, M. et al., , 16: 77 (1979)). (extrachromosomal)
DNA . (bovine papillomavirus)(Sarver, N. et al., Proc. Natl. Acad. Sci., USA, 79: 7147 (1982)), (polyoma virus)(Deans, R. J. et al., Proc. Natl. Acad. Sci., USA, 81 : 1292 (1984)), SV40 (Lusky, M. and Botchan, M., Nature, 293: 79 (1981)) .

[0103] cDNA mRNA ,
RNA mRNA .
(splice signal), (inducible promoter)
(transcription promoter), (enhancer) (termination signal) .
cDNA Okayama, H. and Berg, P., Mol. Cell Biol., 3: 280 (1983); Cepko, C. L. et al., Cell, 37: 1053 (1984); Kaufman, R. J., Proc. Natl. Acad. Sci., USA, 82: 689 (1985)
.

[0104] , . 2
, , . ,
(,) CD200 ,
, , - .

[0105] . ,
2 / - (co-expression) , 2
(Milstein and Cuello, Nature, 305:537-539 (1983)).
(-) . ,
, CH2 CH3 .
, DNA
, - .
, Suresh et al., Methods in Enzymology, 121:210 (1986); WO 96/27011; Brennan et al., Science 229:81 (1985); Shalaby et al., J. Exp. Med. 175:217-225 (1992); Kostelny et al., J. Immunol. 148(5): 1547-1553 (1992); Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993); Gruber et al., J. Immunol. 152:5368 (1994); Tutt et al., J. Immunol. 147:60 (1991) .
- (heteroconjugate) .
- . -

, - U.S. Pat. No. 4,676,980 .

[0106]
. , (leucine zipper) (Kostelny et al., J. Immunol., 148(5): 1547-1553 (1992)). Fos Jun , 2
Fab' .
, - .
. Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993) " (diabody)"
. 2
(pairing) (V_L)
(V_H) . V_H V_L V_L V_H
, 2 - . - Fv(scFv)
(: Gruber et al., J. Immunol., 152:5368 (1994)). ,
Zapata et al. Protein Eng. 8(10): 1057-1062 (1995) " (linear antibody)"
. , Fd (V_H-C_H1-V_H-C_H1)
. .

[0107] , -CD200 -
. -CD200 . -CD200 -CD200
- . (,),
, , (, , PEG), .
(labeling) , , ,
, , (radionuclide) . ,
, , , , (heteroclitic peptide),
, , , (, , RNAi, -
) .

[0108] -CD200 ,
. , , PEG
— , (polyalkylene), (polyalkenylene),
(polyoxyalkylene) . , , , ,
, . - , Fab, Fv, - scFv,
Fab', F(ab')$_2$, F(ab')$_3$.

[0109] **III.**

[0110] **A.**

[0111] 2 - : T ,
- (cell-mediated immunity), B -
. B ,
(invading microbe), , .
.

[0112] - B B T(Th)
Th (Mitchison, Eur. J. Immunol., 1 :18-25 (1971); Claman and Chaperon, Transplant Rev., 1 :92-119 (1969); Katz et al, Proc. Natl. Acad. Scl. USA, 70:2624-2629 (1973); Reff et al., Nature, 226: 1257-1260 (1970)). Th (thymus)-
. Th (, IL-4 IL-5) B
, B B Th (contact)-
(Hirohata et al., J Immunol, 140:3736-3744 (1988); Bartlett et al., J. Immunol, 143:1745-1765 (1989); Brian, Proc. Natl. Acad. Scl. USA, 85:564-568 (1988); Hodgkin et al., J. Immunol, 145:2025-2034 (1990); Noelle et al, J. Immunol, 146:1118-1124 (1991)).

[0113] -CD200 B . ,
-CD200 (, IgG IgM)
.

[0114] , CD200- ,
. , -CD200
- .

[0115] , -CD200 B . , -CD200
B / , - B / .
B . ,
-CD200 IgG / IgM .

[0116] , -CD200 , B
ADCC, CDC / (apoptosis) . , , , ,
, - -CD200 - . ,
. , ,
, .

[0117] ,
. , (GVHD)
, CD200 CD200R
, , -CD200 . ,
. ,
.

[0118] , , , -CD200 (, -CD200)
, . ,
, , (radiation therapy), (high-dose immunomodulatory therapy), (splenectomy) .
, , (adriamycin), (azathioprine),
(busulfan), (cyclophosphamide), (cyclosporine) A, (cytoxan),
(fludarabine), 5- (fluorouracil), (methotrexate),
(mycophenolate mofetil), - , (rapamycin), (sirolimus),
(tacrolimus) . , , OKT3™(muromonab-CD3), CAMPATH™-1G, CAMPATH™-1H(alemtuzumab), CAMPATH™-1M, SIMULEC™(basiliximab), ZENAPAX™(daclizumab),
RITUXAN™(rituximab), - (thymocyte globulin) .

[0119] -CD200 , -CD200
, GVHD (regimen)
, . , -CD200
(allogeneic graft) ,
. -CD200 , GVHD (prophylaxis) ,
, CD200+ - - .

[0120]
. , , -
HLA . ,
, (panel reactive) .
-HLA ,
.
, ,
(clinical criteria) . ,
, , -
(latent humoral response) . -

and C4d (silent reaction), - , C4d
, (subclinical rejection) . ,
(clinical indication),
, - , C4d , ,
.

[0121] -CD200 , ,
. , , , .
, , , , (pancreatic islet
cell) , , , , ,
, . , , ,
, . , , , ,
, , , , , .
, , , . ,
-CD200 (artificial joint), (stent),
(pacemaker device) -
.

[0122] (,)
, , , CD200 CD200R
, , -CD200 .
, B / (, IgG / IgM)
.

[0123] B.

[0124] - CD4+ T (Th) T , ,
T (, CD8+ T) , . (,
) , T Th1 Th2 . Th1 IFN-γ IL-2 , - . Th1 ,
(, (autoimmune hemolytic anemia))
. Th2 IL-4 , -
(, B -), , (,)
. Th2 , . ,
, , .
, , , T .

[0125] , T T
. T (immunological tolerance)
. IL-2, IL-4, IL-5, IL-12 T . T
T , TNFα, TGFβ, IFN-γ, IL-10 . TGFβ T
, Th1 Th2 ,
, Th1 Th2 1 (order of magnitude) . T
CD4+CD25+ (: Waldmann and Cobbold. 2001 Immunity 14:399). T
(activating signal)(,), MHC
(, -CD3 , -CD28) Th1, Th2, T
.

[0126] -CD200 CD4+ CD8+ T
. CD200- ,
. , -CD200
- .

[0127] , -CD200 T / , T
. , -CD200 Th1 / Th2 ,

CD200- T / . T , Th2 B ( ). T -CD200 B / .

[0128] , -CD200 , T ADCC, CDC / (apoptosis) . T . , , , , , - -CD200 - . , .

[0129] , . , (GVHD) , -CD200 . , . , T- .

[0130] , -CD200 -CD200 , . , , , (radiation therapy), (high-dose immunomodulatory therapy)(, T), (splenectomy) . , , (adriamycin), (azathioprine), (busulfan), (cyclophosphamide), (cyclosporine) A, (cytoxan), (fludarabine), 5- (fluorouracil), (methotrexate), (mycophenolate mofetil), - , (rapamycin), (sirolimus), (tacrolimus) . , , OKT3™(muromonab-CD3), CAMPATH™-1G, CAMPATH™-1H(alemtuzumab), CAMPATH™-1M, SIMULEC™(basiliximab), ZENAPAX™(daclizumab), RITUXAN™(rituximab), - (thymocyte globulin) .

[0131] T- -CD200 , -CD200 , GVHD (regimen) , . , -CD200 T , , T .

[0132] **C. CD200**

[0133] , CD200- CD200 . , CD200 . CD200 (, CD200-) . , CD200- .

[0134] , CD200 CD200R , / . CD200- (knockout) , (immunogenic stimuli) (Hoek et al. Science 2000), CD200- (shift) . , CD200- Th1 Th2 . CD200- , CD200- (immune cell attack) . , CD200 . , -CD200 CD200- , CD200- . , CD200:CD200R . , CD200- , CD200- .

[0135] , , , , -CD200 CD200- ADCC / CDC . ADCC /

CDC -CD200 ADCC / CDC
-CD200 .

[0136] IV.

[0137] CD200- /
. CD200- , -CD200 ,
. , -CD200 ,
- , , CD200- CD200- , ,
.
, -CD200 CD200-
(,) - (cell death) CD200-
.

[0138] , CD200- , (,)
. , -CD200
- . , , , , - -CD200
. CD200-
.

[0139] , -CD200 CD200- , T- , B-
, CD200 . ,
-CD200 , ,
. -CD200
, (, -CD200 , , TNF-α INF-γ
), / , T- .

[0140] , ,
. -CD200 CD200- , ,
(acceptance) CD200- ,
. ,
-CD200 .

[0141] -CD200 , ,
, . , ,
.

[0142] , MHC (mismatch) . ,
MHC HLA . , ABO
.

[0143] CD200- .
, (transplant survival)
. , CD200- (,
-CD200) . CD200-
. , CD200
. , , , , ,
, , , , , , (LNA)
, (PNA) , , - , ,
. , , / -
.

[0144] , , - , , - , ,
CD200- (, -CD200
-) . (, (prednisone),
(dexamethasone) (predisolone)), (methotrexate),

(methylprednisolone), (macrolide immunosuppressant)(, (sirolimus)
(tacrolimus)), (, (azathioprine),
(cyclosphamide) (methotrexate), T (,
(cyclosporine)), (mycophenolate mofetil), (glatiramer
acetate), DNA- (, (chlorambucil)) . ,
OKT3(muromonab-CD3), (azathioprine), (leflunomide),
(brequinar), ATG, ALG, 15- (deoxyspergualin), LF15-0195(Tesch et al. Kidney Int. 2001
60(4): 1354-65; Yang et al. J. Leukocyte Biol. 2003;74:438-447), CTLA-4-Ig(belatacept),
(rituxan), IVIg (bredinin) . (thalidomide) ,
, (lenalidomide)(Revlimid, CC-5013) CC-4047(Actimid)
. , , -CD200 -2 α-
IgG1 ,
(, -T) .
. , CD200- (,
) .

[0145] , . , , ,
(plasmapheresis), (splenectomy) (immunoadsorption) -CD200
. , -CD200 .

[0146] , -CD200 .
(cyclosporine) A, (tacrolimus), (rapamycin), -T ,
(daclizumab), (muromonab)-CD3 .
, -CD200 (,
, ,)
. , (, (day), (month), (year)
) 15%, 20%, 25%, 30%, 40%,
50% .

[0147] , -CD200 T (combination treatment)
. , 5 , 7.5 ,
10 . , -CD200 - T
(accommodation) .

[0148] , T
(cytokine profile) , -CD200 , T
. , -CD200
(, A)
.

[0149] , CD200- , , -CD200 -
(, , , FK-506)
.

[0150] , -CD200 /
. (single dose), (multiple dose) .
, -CD200 , ,
. , -CD200
, .

[0151] , .
. (,
) . , , ,
. , ,
.

[0152] - , , , ,
, . , ,
, α- .
, A , - , A((*Pseudomonas aeruginosa*)), (ricin) A , (abrin) A , (modeccin) A , -
(alpha-sacrin), (Aleurites fordii) , (Dianthin) ,
(*Phytolacca americana*) (PAP, PAPII PAP-S), (Momordica charantia) , (curcin),
(crotin), (Saponaria officinalis) , (gelonin),
(mitogillin), (restrictocin), (phenomycin) (enomycin)
. WO85/03508 .
, (adriamycin), (chlorambucil), (daunomycin),
(methotrexate), (neocarzinostatin), .
, .

[0153] , , / .
CD200 2
. , CD200 , 1
, CD200 . CD200 . CD200
. , CD200
, , CD200 .

[0154] V.

[0155] (, ,)
(intravenous), (intraperitoneal), (intracerebral), (intramuscular),
(subcutaneous), (intraocular), (intraarterial), (intrathecal),
, (sustained release system) , , , .
, (bolus injection) .
.

[0156] (ly acceptable carrier) .
"Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition . ,
, , ( ) . ,
. , ,
, pH, (isotonicity) .
, .
.

[0157] , -CD200
. , , - -CD200 , - -
. , , , ,
- -CD200 , - .
, , T .

[0158]
. , (therapeutically effective amount)
, ,
, , .
, .
.

[0159] , (,) ,
CD200-
. , . ,

(, -CD200)
. , (, -CD200)
. , -CD200
- . ,
, , .

[0160] , CD200- (lyoprotectant)
. ,
. , ,
. , CD200- , , -CD200
,
. ,
,
. , -CD200
,
. / (unit dosage form)
. ,
, , ,
. , , .
, / , CD200- , , -
CD200 . ,
, , CD200- , , -CD200 .
,
.

[0161] CD200 CD200R
.

[0162]

1A-1F chC2aB7-hG1 (SEQ ID NO: 1, 2, 3, 4, 5 6) . 1C SEQ ID NO: 3( ) SEQ ID NO: 1( ) . , SEQ ID NO: 3
. 1F SEQ ID NO: 6( ) SEQ ID NO: 4( ) . SEQ ID NO:5(1E) SEQ ID NO:4(1D) .

2A-2F chC2aB7-hG2G4 (SEQ ID NO: 7, 8, 9, 10, 11, 12, 13 14) . 2C SEQ ID NO: 10( ) SEQ ID NO: 9( ) . SEQ ID NO: 9 SEQ ID NO: 7 1- 337 . , SEQ ID NO: 10 . 2F SEQ ID NO: 14( ) SEQ ID NO: 13( ) . SEQ ID NO: 12(2E) SEQ ID NO:11(2D) .

3A-3F hB7V3V2-hG1 (SEQ ID NO: 15, 16, 17, 18, 19 20) . 3C SEQ ID NO: 17( ) SEQ ID NO: 15( ) . 3F SEQ ID NO: 20( ) SEQ ID NO: 18( ) . SEQ ID NO: 19 (3E) SEQ ID NO: 18(3D) .

4A-4F hB7V3V2-hG2G4 (SEQ ID NO: 21, 22, 23, 24, 25 26) . 4C SEQ ID NO: 23( ) SEQ ID NO: 21( ) . , SEQ ID NO: 23

. 4F SEQ ID NO: 26( ) SEQ ID NO: 24( ) . SEQ ID NO:25(4E) SEQ ID NO:24(4D) .

5 T- CD200 . CD3+ mOKT3 , , , CD25, CD200, CD5, CD4 CD8 (fluorochrome)- . , CellQuest FACSCalibur (flow cytometer) (immunofluorescence) . T CD200 (upregulation) .

6 T- ADCC -CD200 . CD3+ T 72 10 / (-) mOKT3 . T , CD56+(NK) . -CD200 (V3V2-G1), -CD200 (V3V2-G2G4) , 25:1(A) 10:1(B) : 37 4 . (lysis) . -CD200 T- ADCC , -CD200 ADCC .

7A-B T (A) -CD200 , . 7A , - IgG . 7B , - IgM . MFI .

8 -CD200 A , CD4+ CD8+ T . .

9A-C -CD200 A , CD3CD200; CD3CD200R, CD19CD200, CD19CD200R, CD11cCD200, CD11cCD200R .

10 OX90NE(SEQ ID NO:27) OX90mG2a(SEQ ID NO:28) . 4 (236, 319, 321 323). 1-118 . 119-448 .

11 OX90 CD200R1 CD200 , (blocking antibody) .

[0163] VI.

[0164] 1

[0165] hB7V3V2 T

[0166] (, IgG1) -CD200 , T T , T .

[0167] A) CD3+ T

[0168] (PBL) Accuspin™System (density gradient centrifugation) . 15 Histopaque-1077(Sigma, St. Louis, MO; cat# H8889) Accuspin (Sigma, St. Louis, MO; cat# A2055) , , Histopaque (frit) 1500 rpm 2 . 30 , (brake) 15 2000 rpm . PBL , 2% - (FBS) PBS(Atlas Biologicals, Ft. Collins, CO; cat# F-0500-D) 2 1200 rpm 10 . CD3+ T

, HTCC-5 (R&D Systems) . , , 5% - , 2 mM L- , 10 mM Hepes / RPMI 1640 .

[0169] B. - mOKT3

[0170] 12- (Falcon) PBS 10 / mOKT3(Orthoclone) 4 . , PBS . CD3+ T 5% - , 2 mM L- , 10 mM Hepes / RPMI 1640 $2x10^6$/ . 5% CO_2 (humidified incubator) 37 72 .

[0171] C. mOKT3- CD3+ ^{51}

[0172] , mOKT3- CD3+ , , - RPMI 1640 10^7 / . 37 2 125 μCi ^{51} (Perkin Elmer, Billerica, MA)/10^6 . , 5% - RPMI , $2x10^5$ / .

[0173] D. NK

[0174] (PBL) . PBL , 2% - (FBS) PBS(Atlas Biologicals, Ft. Collins, CO; cat# F-0500-D) 2 1200 rpm 10 . CD56+ , -CD56- (Miltenyi Biotec, Auburn, CA, Cat # 120-000-307) (positive selection) . , , 5% - , 2 mM L- , 10 mM Hepes / RPMI 1640 $1.3x10^6$ / . 3 $4x10^6$ / 5% CO_2 37 . , , , , 2 mM L- , 10 mM Hepes, 2 x 10^{-5}M 2- / - RPMI .

[0175] E. ADCC

[0176] ^{51}Cr- mOKT3- CD3+ 96- 50 10^4 / . CD56+ , , , $2.5x10^6$ / (25:1 :) 10^6 / (10:1 :) , (100 /). -CD200 (V3V2-G1 V3V2-G2/G4) 10 10, 1, 0.1 0.01 / . (Assay control) : 1) (0 Ab) ; 2) ( ) ; 3) 0.2% Tween-80( ) . . 5% CO_2 37 4 . , , 150 (scintillation vial) (gamma scintillation counter)(Wallac) . , (percent specific lysis) :

[0177]
$$\frac{(\text{분당평균샘플수}(cpm)-\text{평균자발적용해})}{(\text{평균최대용해}-\text{평균자발적용해})}x100$$

[0178] F.

[0179] 100 (mOKT3 - CD3+ CD56+ NK) 96- (Falcon, Franklin Lakes NJ; cat# 353077) . (FITC)-, (PE)-, PerCP-Cy5.5-, (APC)- (Becton-Dickinson, San Jose, CA); - CD25-FITC(cat# 555431); - CD3-APC(cat# 555335); - CD200-PE(cat# 552475); - CD8-PerCP-Cy5.5(cat# 341051); - CD4-APC(cat# 555349); - CD5-APC(cat# 555355) - CD56-APC(cat# 341025) , 4 30 . . FACS 2 (3 1800 rpm) , 300 PBS(Mediatech, Herndon, VA; cat# 21-031-CV) , FacsCaliber Quest (Becton Dickinson, San Jose, CA) .

[0180] 5 , T CD200 . T NK , hB7V3V2-G1 hB7V3V2-G2G4 (6). -CD200 T . .

[0181] T , (negative immunoregulatory role) (Wei S, et al., Cancer Res. 2005 Jun 15; 65(12):5020-6). , -CD200 .

[0182] 2

[0183] **-CD200 mAb .**

[0184] (calcineurin) , , A(CsA) . , (nephrotoxicity) (Seron, D., and F. Moreso. 2004, Transplant Proc 36:257S). (subtherapeutic level) CsA , (Seron, D., and F. Moreso, 2004. Transplant Proc 36:257S; Dunn et al., 2001, Drugs 61:1957; Scott et al. 2003 Drugs 63:1247). (therapy regimen) CsA CsA .

[0185] C57BL/6- -BALB/c MHC- . 5 . :

[0186] - -CD200 mAb: 100 / /day, 0 - 14 , i.p.

[0187] - (Rapa): 2 /kg/day, 0 - 13 ,

[0188] - A(CsA):

[0189] / : 5 /kg/day, 0 - , s. c.

[0190] / : 15 /kg/day, 0 - , s. c.

[0191] / : 15 /kg/day, 0 - 28 , s.c.

[0192] -CD200 mAb European Collection of Cell Cultures(ECACC No. 03062502; Hoek et al., Science 290:1768-1771 (2000)) - CD200 mAb OX90 OX90mG2a . IgG2a kappa . 1 2 . 2 OX90NE . OX90NE - CD200 . OX90mG2a 4 ( ). OX90mG2a OX90NE 10 . OX90 11 , (blocking antibody) . CD200 A20 20 / 12B4( ) OX90 4 30 . R-PE 10 / CD200R1-Fc(Invitrogen/molecular probes, Z 25155) 4 30 . . , OX90hG2G4, OX90NE OX90mG2a A20 CD200 R-PE CD200R1-Fc , 12B4 .

[0193] _______________

[0194] , 10% (formaldehyde) , (paraffin) (embedding) , (hematoxylin) (eosin)(H&E) . 1 (severity) (blinded fashion) (B. G.). (vasculitis), (thrombosis), (hemorrhage) (lymphocyte infiltration) , : 0, ; 1, ; 2, ; 3, ; 4, .

[0195] ____________

[0196] 4 (micrometer) Tissue-Tek Optimum Cutting Temperature(O. C. T.) (Skura Finetek, Torrance, CA) , - (gelatin-coated glass microscope slide) , Elite Vectastain ABC (Vector Laboratories Inc., Burlingame, CA) (avidin)- (biotin) (immunoperoxidase) . (specimen) , - - CD4 mAb(YTS 191.1.2, Cedarlane Laboratories Ltd., Hornby, Ontario, Canada) - - CD8 mAb(53-6.7, BD Biosciences, Franklin Lakes, NJ) $CD4^+$ $CD8^+$ T . (monocyte)/ (macrophage) - - Mac-1 mAb(Cedarlane) . IgG IgM , - - -IgG - -IgM(Cedarlane) . (complement deposition) , - C3 - C5 (Quidel, San Diego, CA), - IgG(Vector Laboratories), HRP- - (streptavidin)(Zymed Laboratories, South San Francisco, CA) . - (phosphate-buffered saline, PBS) (light microscopy) . (negative control) . (antibody reactivity) 5 5 (high-powered field) . 0 4+ : 0, ; 1+, ; 2+, ; 3+, ; 4+, .

1

[0197] :

	(day)	MST ± SD(day)
1)	8, 8, 9, 9 ( )	8.5 ± 0.6
2) CsA(/)	9, 10, 10, 10, 11, 11 ( )	10.1 ± 0.3
3) CsA(/)	15, 16, 16, 17 ( )	16 ± 0.8
4) OX90mG2a	8, 9, 9, 9, 10, 11	9
5) OX90mG2a + CsA (/)	>100 x 4	>100
6) OX90mG2a + CsA (/)	56(B), 71(B), 75(B)	71
7) OX90mG2a + CsA (/)	53, 54, 54, >76(A), >76(A), >81(A-), >81(A-)	>76
8) OX90mG2a + Rapa	>100 x 6	>100

[0198] * : A, ; B, ; C, ; D, (cardiac impulse) . MST = ; SD = .

2

[0199] :

	*	(day)
1) OX90mG2a	9, 10, 10, 11	10
2) OX90mG2a + CsA (/)	13#, 13#, 14#, 31#, 40**, 75, 78	75
3) OX-90NE + CsA (/)	14#, 16#, 39, 39, 64, 67, 68	64
4) (12B4) + CsA(/)	12, 12, 13, 14	12.5

[0200] * : A, ; B, ; C, ; D, (cardiac impulse) .

[0201] **

[0202] # , (batch) .

[0203]

[0204] (12B4) . , (12B4) + CsA CsA . 1 2 -CD200 . .

3

[0205] ( ) *

	Vasc	Infar	Lymph	Throm	Hemo
1) (POD8/)	3.0	3.0	3.0	4.0	3.0
2) CsA(/ , POD16/)	2.0	1.0	2.0	3.0	2.0
3) CsA(/)	3.0	2.0	2.0	4.0	2.0
4) OX90mG2a (POD9/)	2.0	1.0	2.0	3.0	2.0
5) OX90mG2a + CsA (/ , POD100)	0.0	1.0	1.0	1.0	0.0
6) OX90mG2a + CsA (/)	2.0	0.0	2.0	0.0	1.0
7) OX90mG2a + CsA (/)	1.0	1.0	2.0	1.0	1.0
8) OX-90NE + CsA (/)	2.0	1.0	2.0	1.0	2.0

9) (12B4) + CsA (/)	2.0	2.0	2.0	3.0	2.0

[0206] * : 0 - ; 1- ; 2 - ; 3 - ; 4 - . POD = .

[0207] , - T . CsA -CD200 mAb - (7A 7B). , CsA -CD200 mAb CD4+ CD8+ T (8). , : CD3CD200; CD3CD200R; CD19CD200; CD19CD200R; CD11cCD200; CD11cCD200R. 9A-C .

[0208] IgG, IgM, C3 C5, (, CD4, CD8 Mac-1) . 4-6 .

4

[0209] ( ).

( )	IgG	IgM	C3	C5
1)	4+	2+	3+	3+
2) CsA(/)	3+	2+	3+	3+
3) CsA(/)	3+	2+	3+	3+
4) OX90mG2a	2+	2+	3+	3+
5) OX90mG2a + CsA (/ , POD100)	1+	1+	3+	2.5+
6) OX90mG2a + CsA (/)	2+	2+	3+	3+
7) OX90mG2a + CsA (/)	2+	2+	3+	3+
8) OX-90NE + CsA (/)	2+	2+	3+	3+
9) (12B4) + CsA (/)	2+	2+	3+	3+

[0210] : 0 , 1+ , 2+ , 3+ , 4+ .

5

[0211] ( ).

( )	CD4	CD8	Mac
1)	3+	2+	3+
2) CsA(/)	2+	2+	3+
3) CsA(/)	2+	2+	3+

4) OX90mG2a	2+	1+	3+
5) OX90mG2a + CsA (/ , POD100)	1+	1+	1+
6) OX90mG2a + CsA (/)	2+	2+	2+
7) OX90mG2a + CsA (/)	2+	1+	2+
8) OX-90NE + CsA(/)	2+	2+	3+
9) (12B4) + CsA (/)	2+	2+	3+

[0212] : 0 , 1+ , 2+ , 3+ , 4+ .

6

[0213] CD200 CD200R ( ).

( )	CD200	CD200R
1)	3+	2+
2) CsA(/)	3+	2+
3) CsA(/)	3+	2+
4) OX90mG2a	2+	1+
5) OX90mG2a + CsA (/ , POD100)	2+	1+
6) OX90mG2a + CsA (/)	2+	1+
7) OX90mG2a + CsA (/)	2+	1+
8) OX-90NE + CsA(/)	2+	1+
9) (12B4) + CsA (/)	3+	2+

[0214] : 0 , 1+ , 2+ , 3+ , 4+ .

[0215] CsA -CD200 mAb . , -CD200 mAb CsA .

[0216] 3

[0217] **-CD200 mAb, OX90NE-AG**

[0218] OX90NE , , OX90NE , , OX90NE-AG . OX90NE-AG OX90NE Asn 298 Gln . AG (aglycosylation) (Asn298 (glycosylation) Gln298); ADCC CDC .

[0219] , C57BL/6- -BALB/c MHC-

. 5 . :

[0220] - OX90NE-AG: 100 / /day, 0 - 14 , i.p.

[0221] - A(CsA): 15 /kg/day, 0 - , s.c.

[0222] 7 .

7

[0223]

	*
CsA + OX90NE-AG (POD16)	16(A) x 5
CsA + OX90NE-AG (POD100) /	>90(A), >90(A), >90(A), >90(A), >90(A)

[0224] * : A, ; B, ; C, ; D, (cardiac impulse) . MST = ; SD = ; POD = .

[0225] 10 . 5 3-6 16 . 5 90 100 , 3-6 16 100 .

[0226] . , , OX-2/CD200 , . , , . 70% . , 80% . , 90% . , . .

[0227]

[0228] . .

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1a

주의: 리더 서열(AA)은 밑줄로 표시되고 불변 영역은 굵은 글씨체로 표시된다

chC2aB7-hG1

중쇄(hG1에서 인트론)(SEQ ID NO. 1)

MGWSCIILFLVATATGVHSLEVQLQQSGPELVKPGASLKMSCKASGYSFT
DYIILWVKQNHGKSLEWIGHIDPYYGSSNYNLKFKGKATLTVDKSSSTAY
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PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT
CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

1b

(SEQ ID NO. 2) (게놈 서열 hG1)

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GAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG
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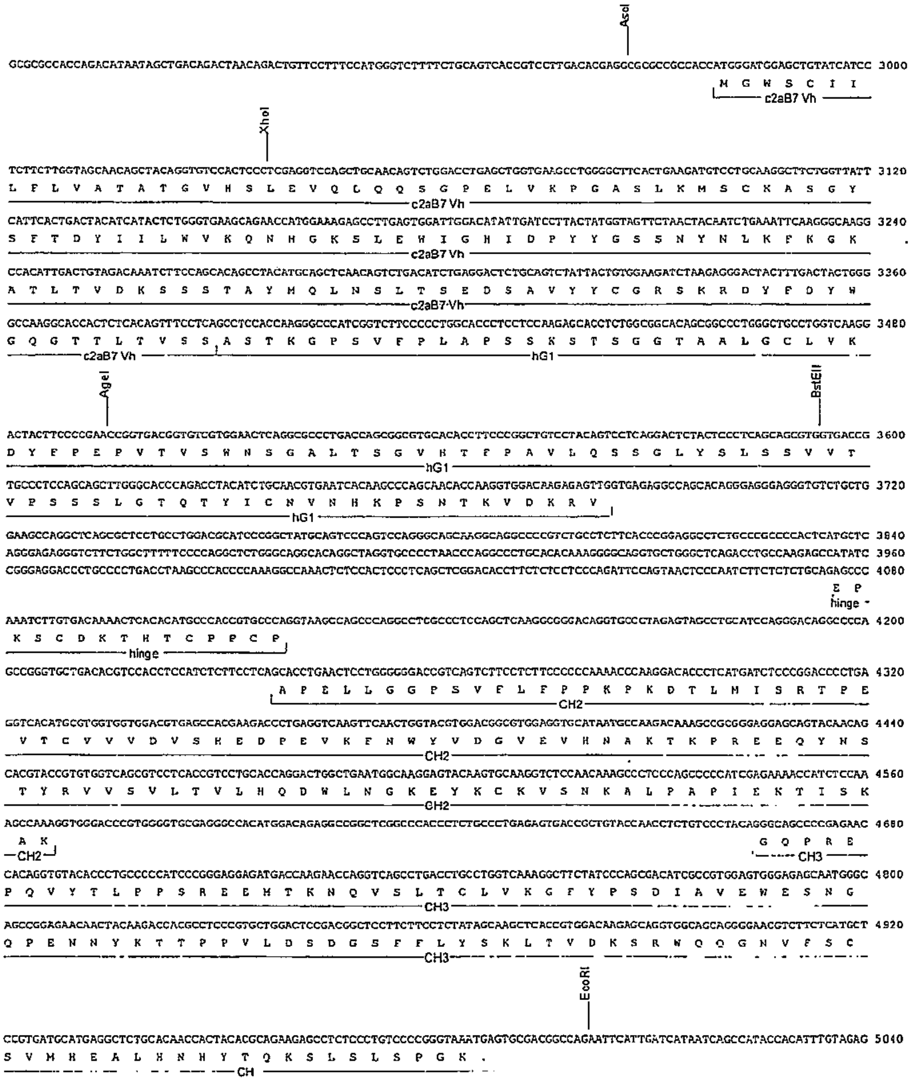
GGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC
CTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCC
GTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCCCCGGGTAAA
TGA

1c

항체 chC2aB7-hG1의 중쇄의 개요도



1d

경쇄(인간 Cκ)(SEQ ID NO. 4)

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YCLQYDEFPYTFGGGTKLEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN**
FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
KHKVYACEVTHQGLSSPVTKSFNRGEC

1e

(SEQ ID NO. 5)

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CAGTGGATCTGGGCAAGATTATTCTCTCACCATCAGCAGCCTGGAGTATG
AAGATATGGGAATTTATTATTGTCTACAGTATGATGAGTTTCCGTACACGT
TCGGAGGGGGGACCAAGCTGGAAATAAAACGGACTGTGGCTGCACCATC
TGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTC
TGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGT
GGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCAC
AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACG
CTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCA
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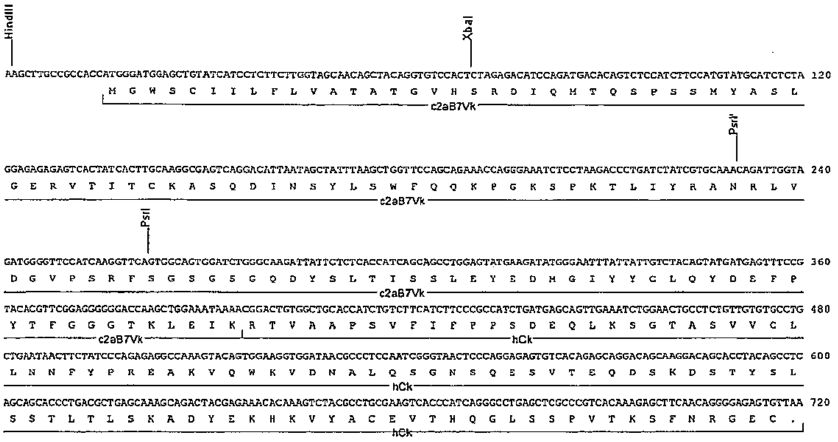
1f

항체 chC2aB7-hG1의 경쇄의 개요도



2a

chC2aB7-hG2G4
중쇄(SEQ ID NO. 7)

MGWSCIILFLVATATGVHS*L*EVQLQQSGPELVKPGASLKMSCKASGYSFT
DYIILWVKQNHGKSLEWIGHIDPYYGSSNYNLKFKGKATLTVDKSSSTAY
MQLNSLTSEDSAVYYCGRSKRDYFDYWGQGTTLTVSS**ASTKGPSVFPLA**
PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECP
PCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
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KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLV
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WQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

2b

(SEQ ID NO. 8) (게놈 서열 hG2G4)

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ACCCTCTGCCCTGGGAGTGACCGCTGTGCCAACCTCTGTCCCTACAGGGCAGCCCCGAGAGCC
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GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
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AGGCTAACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCA
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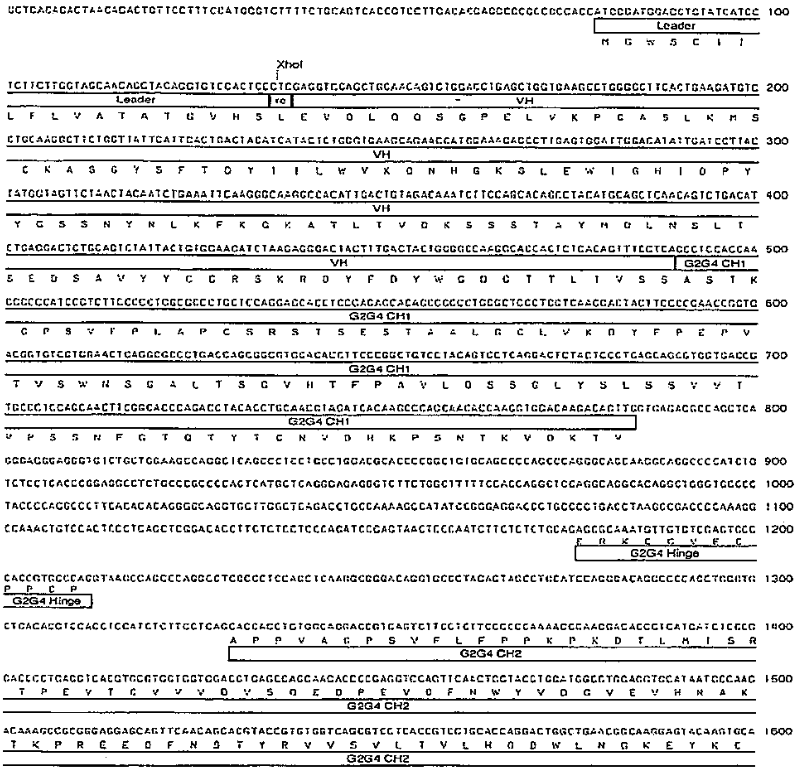
2c

항체 chC2aB7-hG2G4의 중쇄(아미노산 1-337)의 개요도



2d

경쇄(인간 Cκ)(SEQ ID NO. 11)

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2e

(SEQ ID NO. 12)
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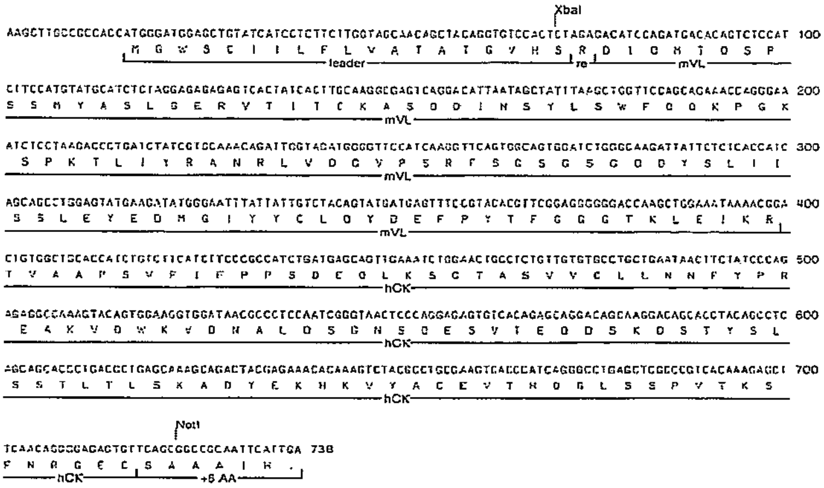
2f

항체 chC2aB7-hG2G4의 경쇄의 개요도



3a

hB7V3V2-hG1
중쇄(SEQ ID NO. 15)
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IILWVRQNPGKGLEWIGHIDPYYGSSNYNLKFKGRVTITADQSTTTAYME
LSSLRSEDTAVYYCGRSKRDYFDYWGQGTTLTVSS**ASTKGPSVFPLAPSS**
KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCP
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3b

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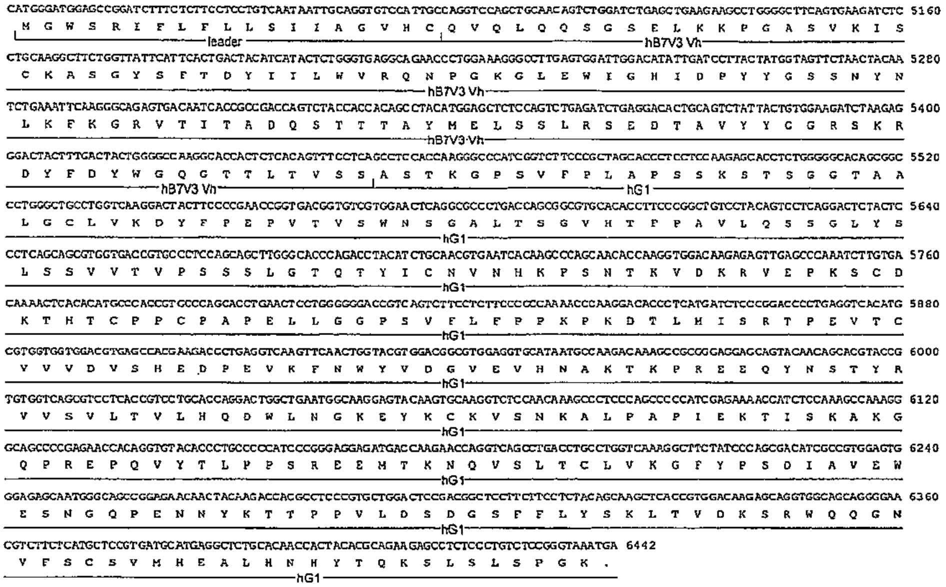
3c

항체 hB7V3V2-hG1의 중쇄의 개요도



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3e

(SEQ ID NO. 19)

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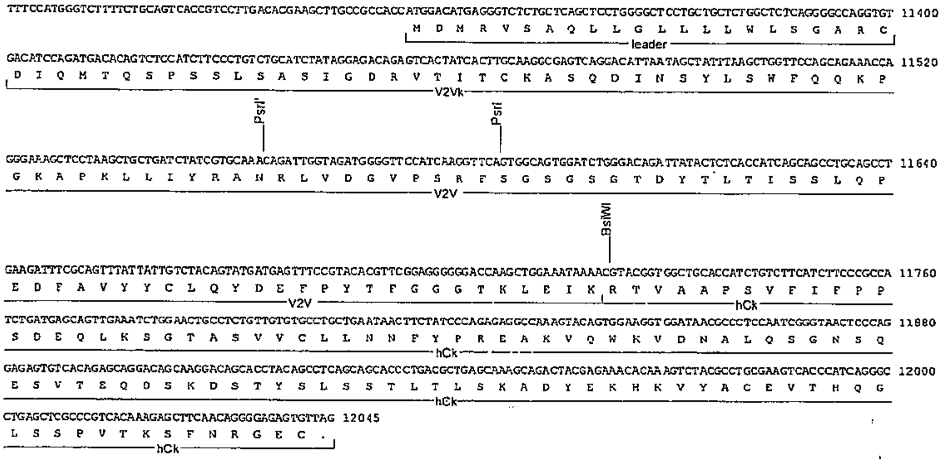
항체 hB7V3V2-hG1의 경쇄의 개요도



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hB7V3V2-hG2G4

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4b

(SEQ ID NO. 22) (게놈 서열 hG2G4)

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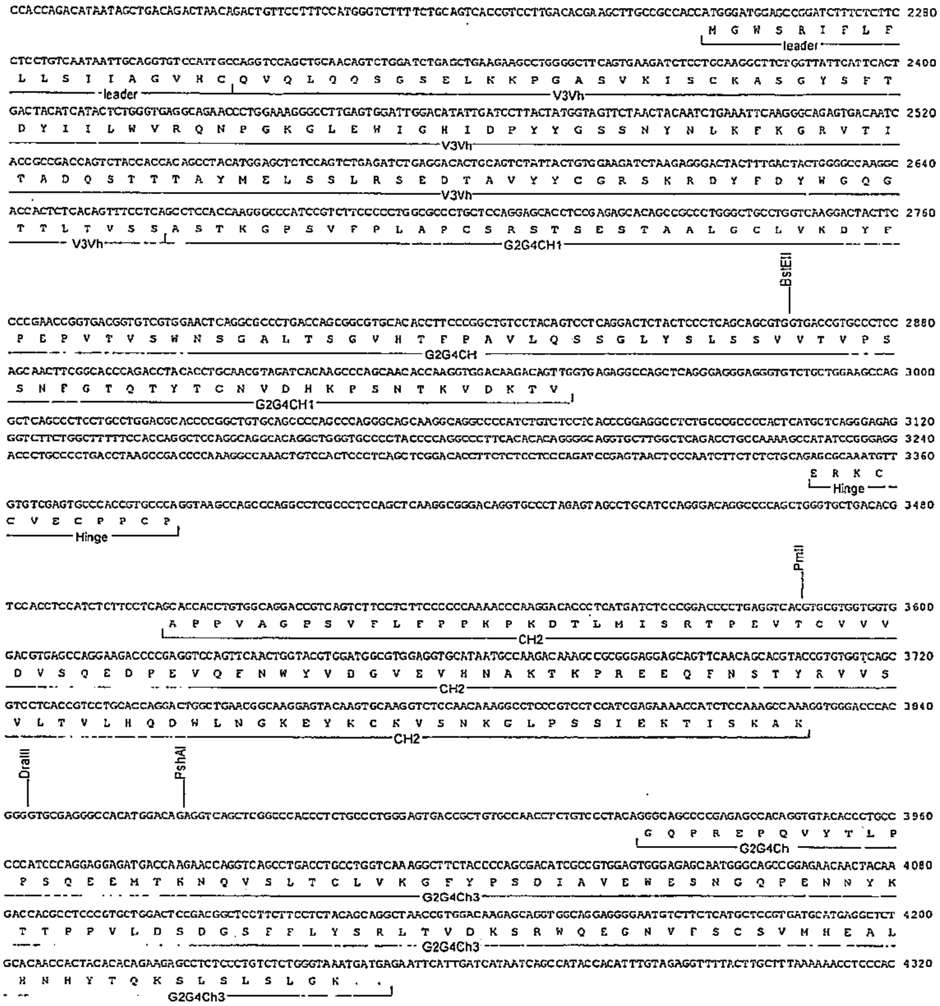
4c

항체 hB7V3V2-hG2G4의 중쇄의 개요도



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경쇄(인간 Cκ)(SEQ ID NO. 24)

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4e

(SEQ ID NO. 25)

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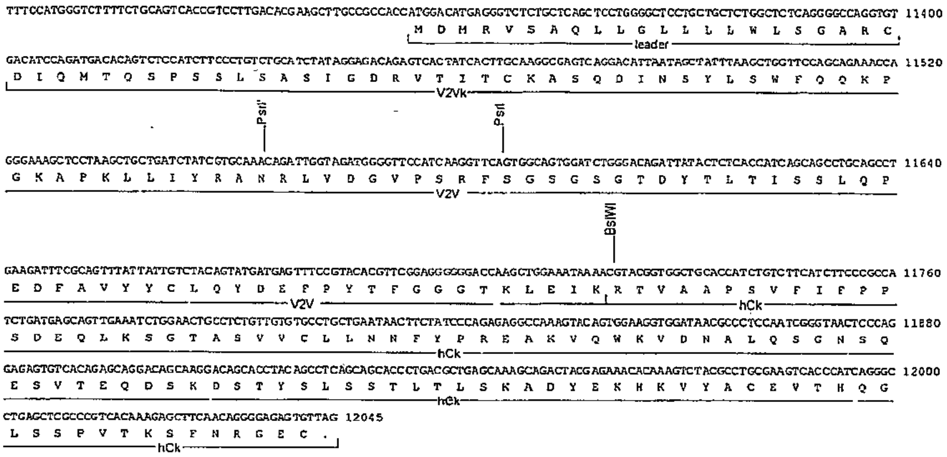
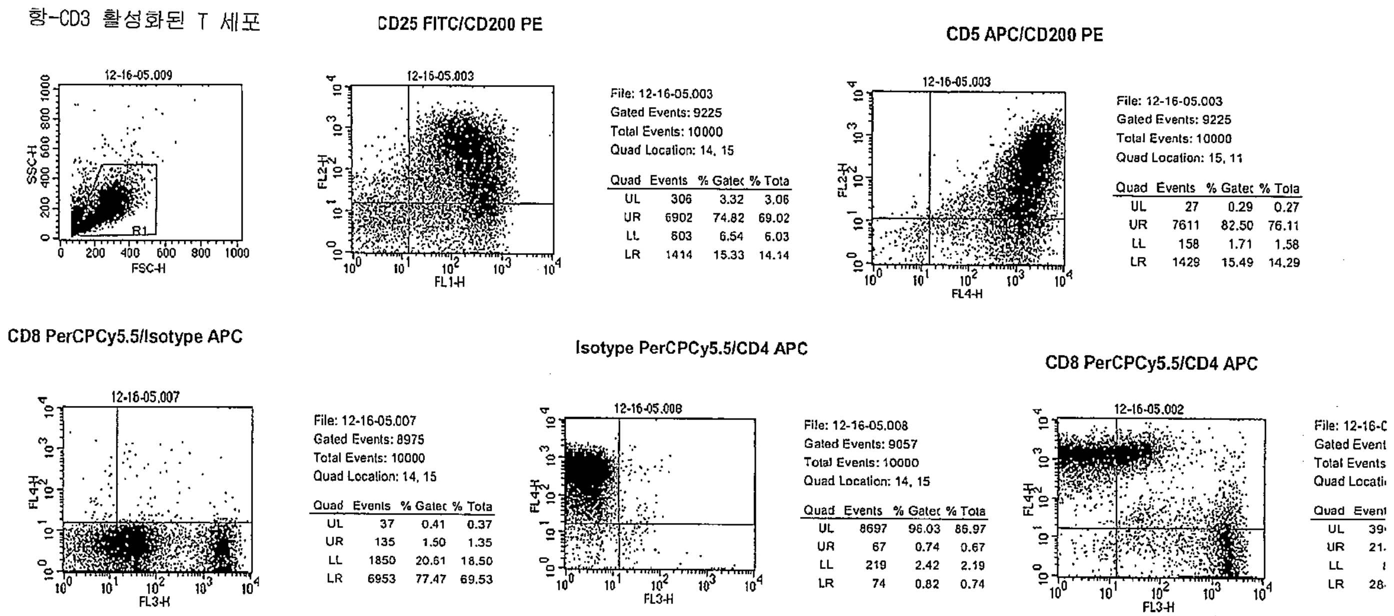
항체 hB7V3V2-hG2G4의 경쇄의 개요도



5

mOKT3으로 활성화 이후에 인간 CD3+ 세포 상에서 CD200의 세포 표면 발현



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Gated Events: 9225
Total Events: 10000
Quad Location: 14, 15

Quad	Events	% Gatec	% Tota
UL	306	3.32	3.06
UR	6902	74.82	69.02
LL	603	6.54	6.03
LR	1414	15.33	14.14

File: 12-16-05.003
Gated Events: 9225
Total Events: 10000
Quad Location: 15, 11

Quad	Events	% Gatec	% Tota
UL	27	0.29	0.27
UR	7611	82.50	76.11
LL	158	1.71	1.58
LR	1429	15.49	14.29

File: 12-16-05.007
Gated Events: 8975
Total Events: 10000
Quad Location: 14, 15

Quad	Events	% Gatec	% Tota
UL	37	0.41	0.37
UR	135	1.50	1.35
LL	1850	20.61	18.50
LR	6953	77.47	69.53

File: 12-16-05.008
Gated Events: 9057
Total Events: 10000
Quad Location: 14, 15

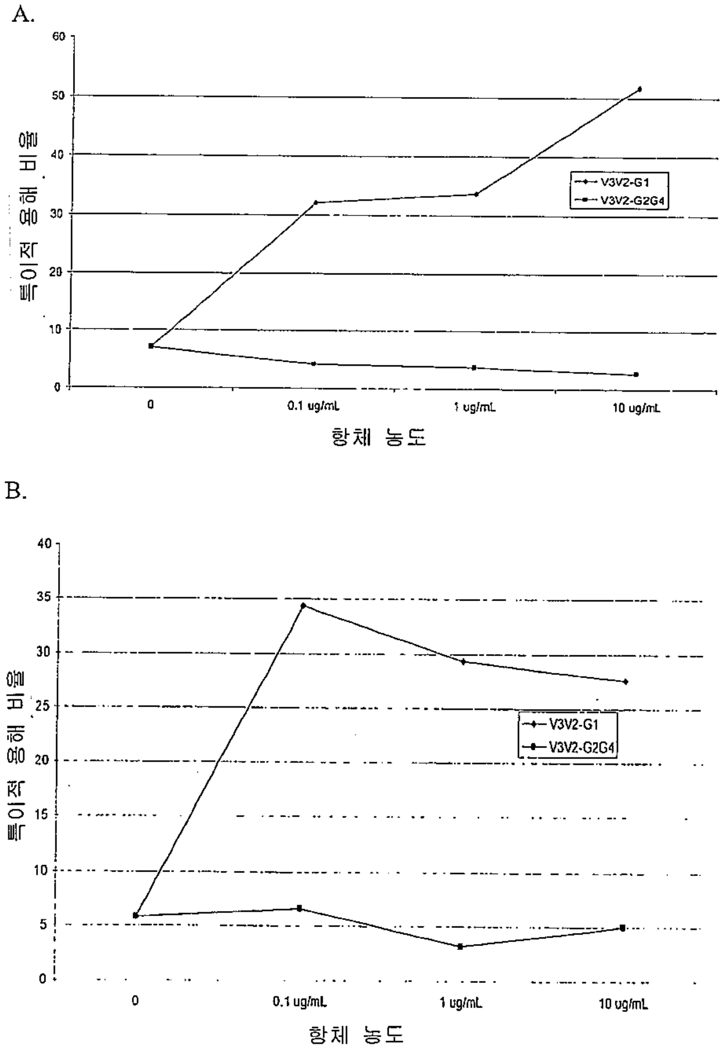
Quad	Events	% Gatec	% Tota
UL	8697	96.03	86.97
UR	67	0.74	0.67
LL	219	2.42	2.19
LR	74	0.82	0.74

File: 12-16-C
Gated Event
Total Events
Quad Locati

Quad	Event
UL	39
UR	21.
LL	
LR	28

6

T-세포 수용체 신호전달을 통하여 활성화된 인간 T 세포는 항-CD200 매개된 ADCC에 대한 감수성 표적으로서 기능한다.



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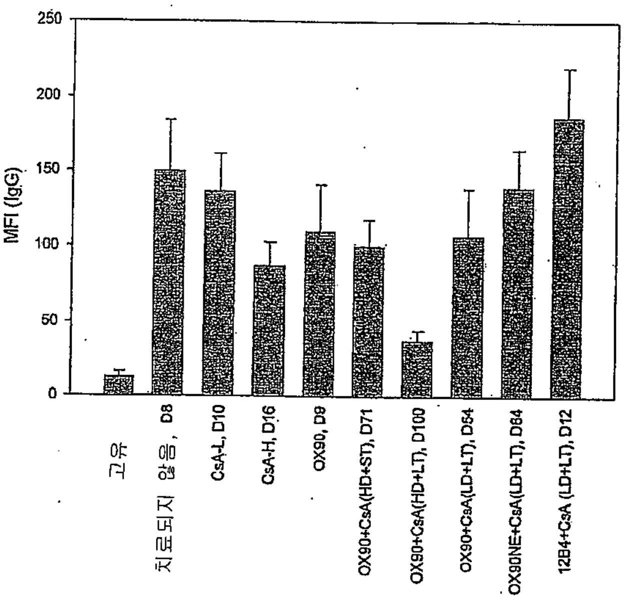
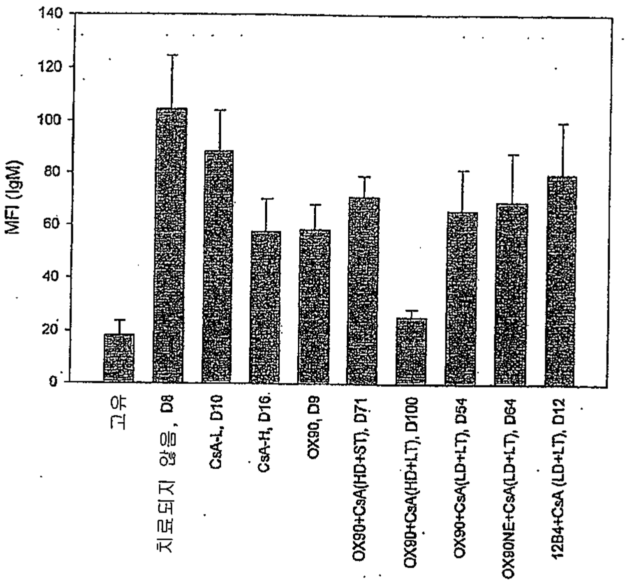


HD = 고용량, LD = 저용량, LT = 장기, ST = 단기
*동물은 거부반응의 종점에서 희생되었다.

7b



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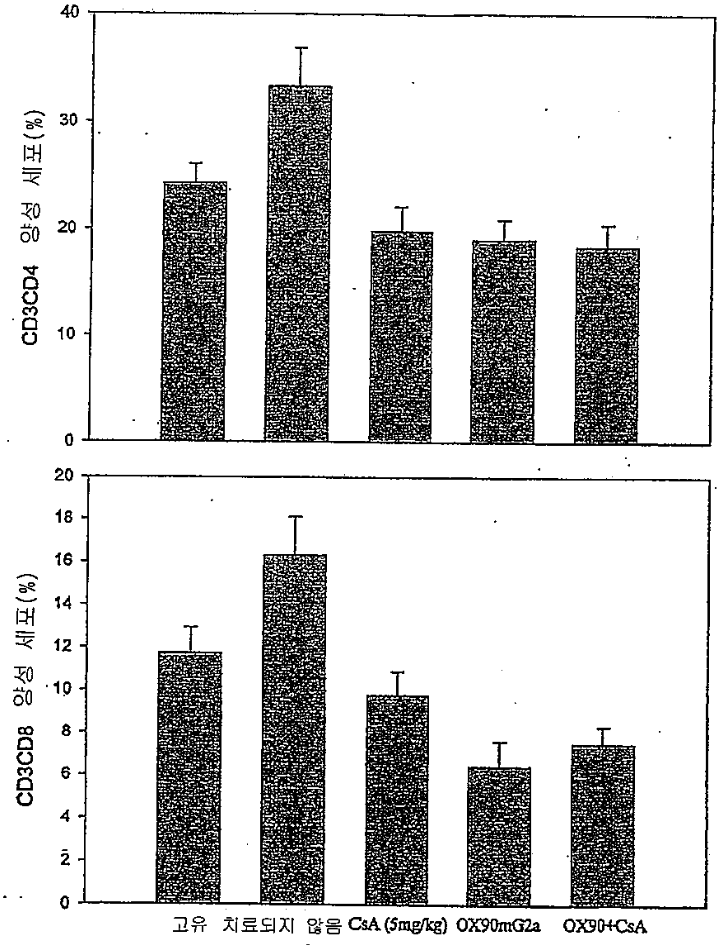
*동물은 거부반응의 종점에서 희생되었다.

8

생쥐 심장 동종이식편 수용자에서 세포 개체군의 비교(OX90 프로젝트)



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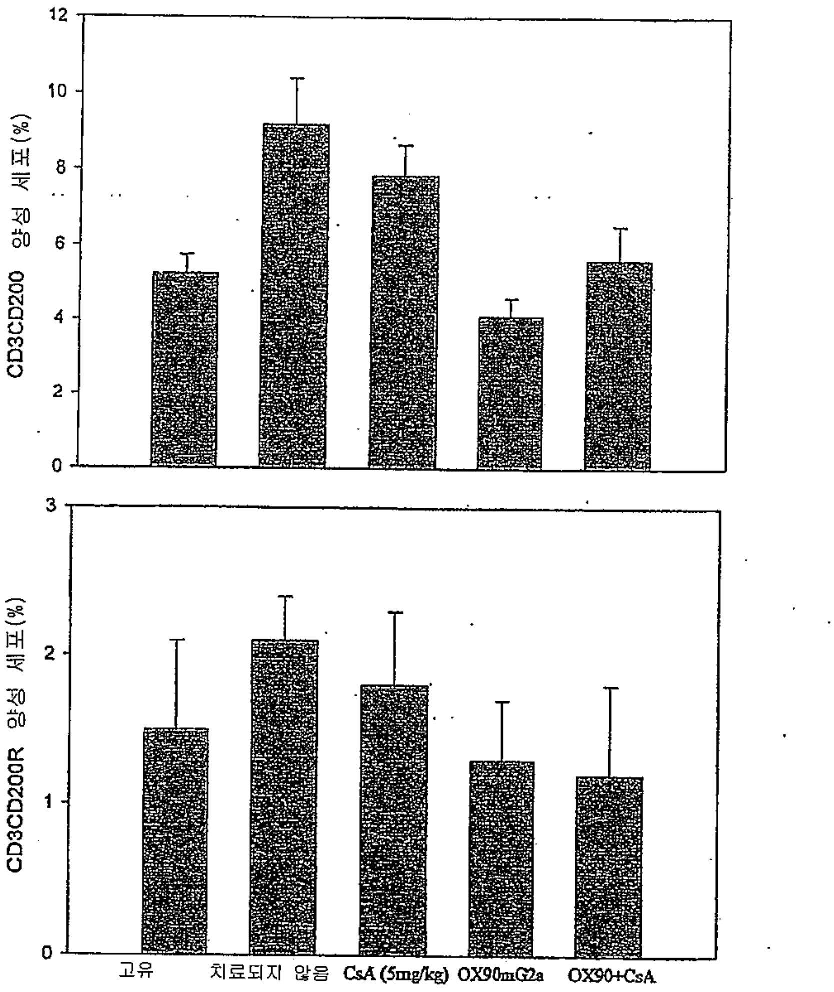
생쥐 심장 동종이식편 수용자에서 세포 개체군의 비교(OX90 프로젝트)



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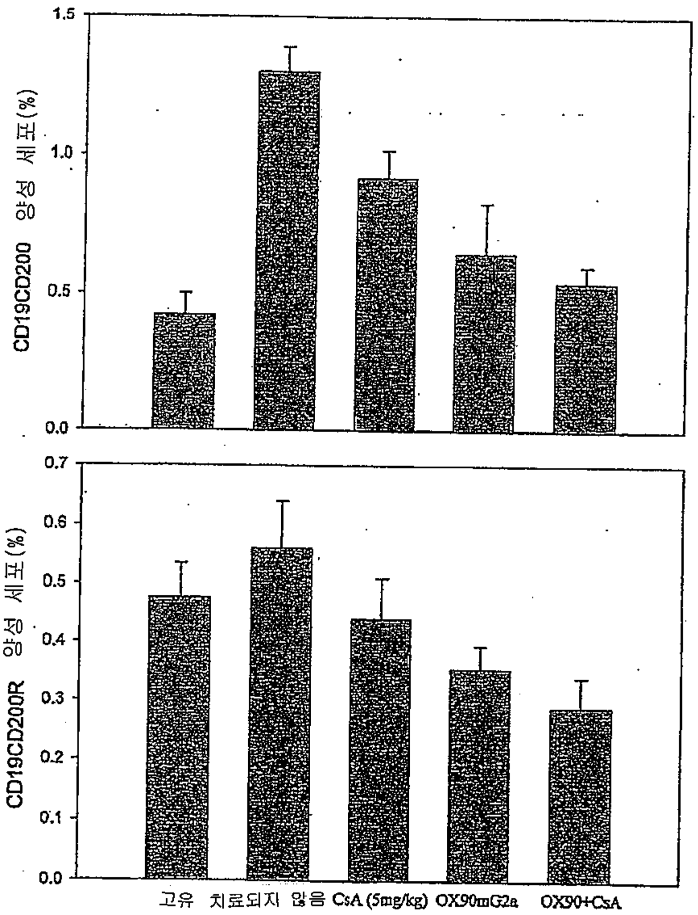

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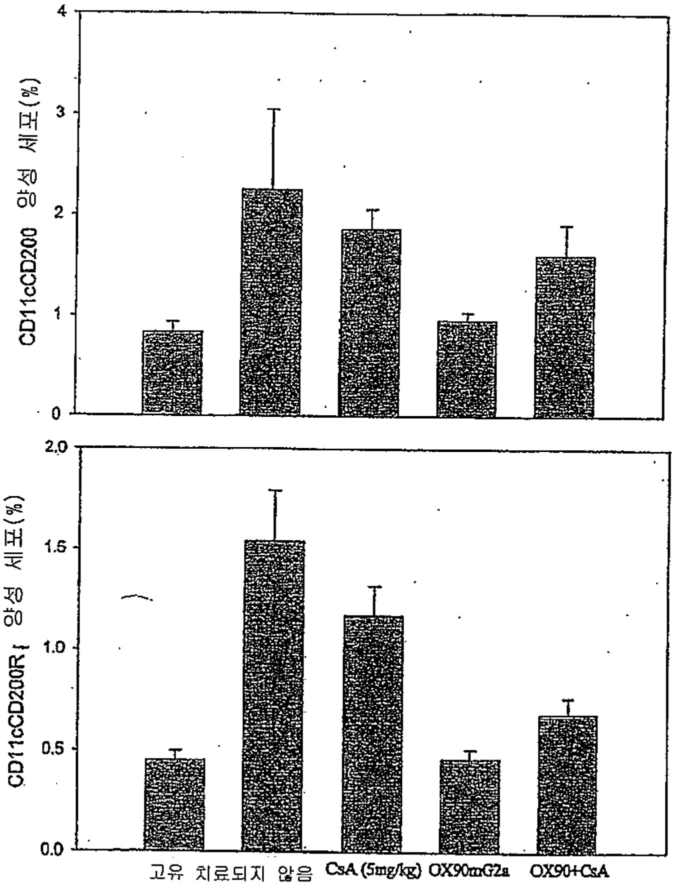

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226	PPCKCPAPNL**L**GGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSED	OX90mg2a
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316	SGK**E**F**K**C**K**VNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMT	OX90mG2a
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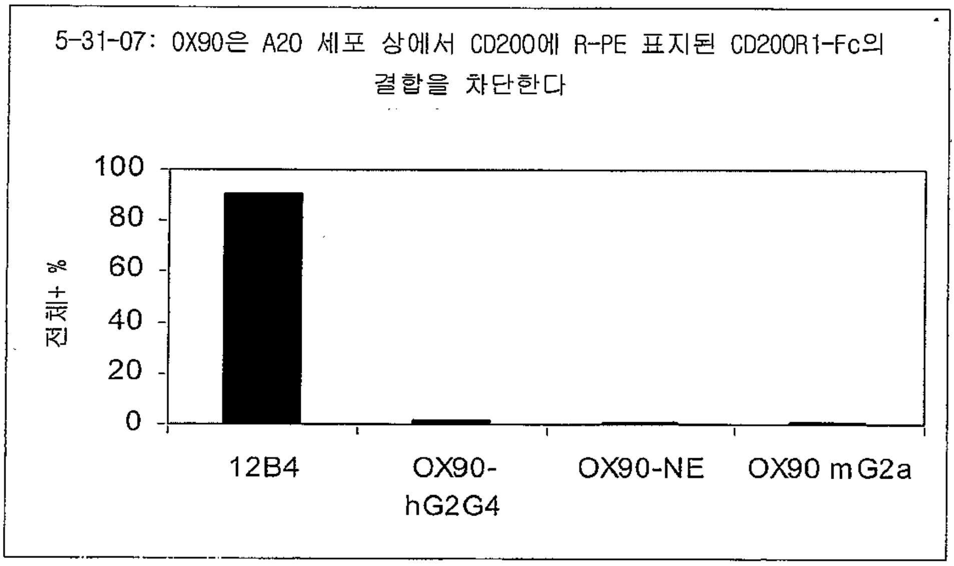
11



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Leu Glu Trp Ile Gly His Ile Asp Pro Tyr Tyr Gly Ser Ser Asn Tyr


65                  70                  75                  80

Asn Leu Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser

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Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly

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Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

385 390 395 400

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

405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val

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ctatgcagtc ccagtccagg gcagcaaggc aggccccgtc tgcctcttca cccggaggcc 840

tctgcccgcc ccactcatgc tcagggagag ggtcttctgg ctttttcccc aggctctggg 900

caggcacagg ctaggtgccc ctaacccagg ccctgcacac aaaggggcag gtgctgggct 960

cagacctgcc aagagccata tccgggagga ccctgcccct gacctaagcc caccccaaag 1020

gccaaactct ccactccctc agctcggaca ccttctctcc tcccagattc cagtaactcc 1080

caatcttctc tctgcagagc ccaaatcttg tgacaaaact cacacatgcc caccgtgccc 1140

aggtaagcca gcccaggcct cgccctccag ctcaaggcgg gacaggtgcc ctagagtagc 1200

ctgcatccag ggacaggccc cagccgggtg ctgacacgtc cacctccatc tcttcctcag 1260

cacctgaact cctgggggga ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc 1320

tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc 1380

ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc aagacaaagc 1440

cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc 1500

aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc ctcccagccc 1560

ccatcgagaa aaccatctcc aaagccaaag gtgggacccg tggggtgcga gggccacatg 1620

gacagaggcc ggctcggccc accctctgcc ctgagagtga ccgctgtacc aacctctgtc 1680

cctacagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 1740

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 1800

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 1860

gactccgacg gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag 1920

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1980

aagagcctct ccctgtcccc gggtaaatga 2010

<210> 3

<211> 2160

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<220><221> CDS

<222> (99)..(803)

<220><221> CDS

<222> (1195)..(1239)

<220><221> CDS

<222> (1358)..(1687)

<220><221> CDS

<222> (1785)..(2105)

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ctgcagtcac cgtccttgac acgaggcgcg ccgccacc atg gga tgg agc tgt atc 116

Met Gly Trp Ser Cys Ile

1 5

atc ctc ttc ttg gta gca aca gct aca ggt gtc cac tcc ctc gag gtc 164

Ile Leu Phe Leu Val Ala Thr Ala Thr Gly Val His Ser Leu Glu Val

10 15 20

cag ctg caa cag tct gga cct gag ctg gtg aag cct ggg gct tca ctg 212

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

25 30 35

aag atg tcc tgc aag gct tct ggt tat tca ttc act gac tac atc ata 260

Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr Ile Ile

40 45 50

ctc tgg gtg aag cag aac cat gga aag agc ctt gag tgg att gga cat 308

Leu Trp Val Lys Gln Asn His Gly Lys Ser Leu Glu Trp Ile Gly His

55 60 65 70

att gat cct tac tat ggt agt tct aac tac aat ctg aaa ttc aag ggc 356

Ile Asp Pro Tyr Tyr Gly Ser Ser Asn Tyr Asn Leu Lys Phe Lys Gly

75 80 85

aag gcc aca ttg act gta gac aaa tct tcc agc aca gcc tac atg cag 404

Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln

90 95 100

ctc aac agt ctg aca tct gag gac tct gca gtc tat tac tgt gga aga 452

Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Gly Arg

105 110 115

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tct aag agg gac tac ttt gac tac tgg ggc caa ggc acc act ctc aca      500
Ser Lys Arg Asp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
    120                 125                 130
gtt tcc tca gcc tcc acc aag ggc cca tcg gtc ttc ccc ctg gca ccc      548


Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
135                 140                 145                 150
tcc tcc aag agc acc tct ggc ggc aca gcg gcc ctg ggc tgc ctg gtc      596
Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
                155                 160                 165
aag gac tac ttc ccc gaa ccg gtg acg gtg tcg tgg aac tca ggc gcc      644
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala


            170                 175                 180
ctg acc agc ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga      692
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
        185                 190                 195
ctc tac tcc ctc agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc      740
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
    200                 205                 210


acc cag acc tac atc tgc aac gtg aat cac aag ccc agc aac acc aag      788
Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
215                 220                 225                 230
gtg gac aag aga gtt ggtgagaggc cagcacaggg agggagggtg tctgctggaa      843
Val Asp Lys Arg Val
                235
gccaggctca gcgctcctgc ctggacgcat cccggctatg cagtcccagt ccagggcagc    903


aaggcaggcc ccgtctgcct cttcacccgg aggcctctgc ccgccccact catgctcagg    963
gagagggtct tctggctttt tccccaggct ctgggcaggc acaggctagg tgcccctaac   1023
ccaggccctg cacacaaagg ggcaggtgct gggctcagac ctgccaagag ccatatccgg   1083
gaggaccctg cccctgacct aagcccaccc caaaggccaa actctccact ccctcagctc   1143
ggacaccttc tctcctccca gattccagta actcccaatc ttctctctgc a gag ccc    1200
                                                         Glu Pro
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aaa tct tgt gac aaa act cac aca tgc cca ccg tgc cca ggtaagccag      1249
Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
        240                 245                 250
cccaggcctc gccctccagc tcaaggcggg acaggtgccc tagagtagcc tgcatccagg   1309
gacaggcccc agccgggtgc tgacacgtcc acctccatct cttcctca gca cct gaa    1366
                                                     Ala Pro Glu
ctc ctg ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac     1414
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    255                 260                 265
acc ctc atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac     1462
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
270                 275                 280                 285
gtg agc cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc     1510
Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                290                 295                 300
gtg gag gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac     1558
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
            305                 310                 315
agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg     1606
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        320                 325                 330
ctg aat ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca     1654
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    335                 340                 345
gcc ccc atc gag aaa acc atc tcc aaa gcc aaa ggtgggaccc gtggggtgcg   1707
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
350                 355                 360
```

agggccacat ggacagaggc cggctcggcc caccctctgc cctgagagtg accgctgtac   1767

caacctctgt ccctaca ggg cag ccc cga gaa cca cag gtg tac acc ctg   1817

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu

365   370

ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc ctg acc tgc   1865

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

375   380   385

ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag tgg gag agc   1913

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser

390   395   400

aat ggg cag ccg gag aac aac tac aag acc acg cct ccc gtg ctg gac   1961

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp

405   410   415

tcc gac ggc tcc ttc ttc ctc tat agc aag ctc acc gtg gac aag agc   2009

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser

420   425   430   435

agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct   2057

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala

440   445   450

ctg cac aac cac tac acg cag aag agc ctc tcc ctg tcc ccg ggt aaa   2105

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

455   460   465

tgagtgcgac ggccagaatt cattgatcat aatcagccat accacatttg tagag   2160

<210> 4

<211> 234

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 4

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly

1   5   10   15

Val His Ser Arg Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Tyr

            20   25   30

Ala Ser Leu Gly Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp

        35   40   45

Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro

    50   55   60

Lys Thr Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser

65   70   75   80

Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser

                85   90   95

Ser Leu Glu Tyr Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp

            100   105   110

Glu Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg

        115   120   125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln

    130   135   140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

145   150   155   160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser

                165   170   175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr

            180   185   190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys

        195   200   205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro

    210   215   220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

225   230

<210> 5

<211> 705

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 5

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gacatccaga tgacacagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 120

atcacttgca aggcgagtca ggacattaat agctatttaa gctggttcca gcagaaacca 180

gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggtagatgg ggttccatca 240

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagtat 300

gaagatatgg gaatttatta ttgtctacag tatgatgagt ttccgtacac gttcggaggg 360

gggaccaagc tggaaataaa acggactgtg gctgcaccat ctgtcttcat cttcccgcca 420

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 480

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 540

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 600

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 660

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttaa 705

<210> 6

<211> 720

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<220><221> CDS

<222> (16)..(717)

<400> 6

aagcttgccg ccacc atg gga tgg agc tgt atc atc ctc ttc ttg gta gca 51

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala

1 5 10

aca gct aca ggt gtc cac tct aga gac atc cag atg aca cag tct cca 99

Thr Ala Thr Gly Val His Ser Arg Asp Ile Gln Met Thr Gln Ser Pro

15 20 25

tct tcc atg tat gca tct cta gga gag aga gtc act atc act tgc aag 147

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Ser Ser Met Tyr Ala Ser Leu Gly Glu Arg Val Thr Ile Thr Cys Lys
    30                  35                  40
gcg agt cag gac att aat agc tat tta agc tgg ttc cag cag aaa cca      195
Ala Ser Gln Asp Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro


45                  50                  55                  60
ggg aaa tct cct aag acc ctg atc tat cgt gca aac aga ttg gta gat      243
Gly Lys Ser Pro Lys Thr Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp
                65                  70                  75
ggg gtt cca tca agg ttc agt ggc agt gga tct ggg caa gat tat tct      291
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser
            80                  85                  90


ctc acc atc agc agc ctg gag tat gaa gat atg gga att tat tat tgt      339
Leu Thr Ile Ser Ser Leu Glu Tyr Glu Asp Met Gly Ile Tyr Tyr Cys
        95                  100                 105
cta cag tat gat gag ttt ccg tac acg ttc gga ggg ggg acc aag ctg      387
Leu Gln Tyr Asp Glu Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu
    110                 115                 120
gaa ata aaa cgg act gtg gct gca cca tct gtc ttc atc ttc ccg cca      435


Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
125                 130                 135                 140
tct gat gag cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg      483
Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
                145                 150                 155
aat aac ttc tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac      531
Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn


            160                 165                 170
gcc ctc caa tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc      579
Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
        175                 180                 185
aag gac agc acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca      627
Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
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190 195 200

gac tac gag aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc 675

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly

205 210 215 220

ctg agc tcg ccc gtc aca aag agc ttc aac agg gga gag tgt taa 720

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

225 230

<210> 7

<211> 463

<212> PRT

<213> Artificial Sequence

<

220><223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 7

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly

1 5 10 15

Val His Ser Leu Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val

20 25 30

Lys Pro Gly Ala Ser Leu Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser

35 40 45

Phe Thr Asp Tyr Ile Ile Leu Trp Val Lys Gln Asn His Gly Lys Ser

50 55 60

Leu Glu Trp Ile Gly His Ile Asp Pro Tyr Tyr Gly Ser Ser Asn Tyr

65 70 75 80

Asn Leu Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser

85 90 95

Ser Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala

100 105 110

Val Tyr Tyr Cys Gly Arg Ser Lys Arg Asp Tyr Phe Asp Tyr Trp Gly

115 120 125

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

```
    130                 135                 140

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala

145                 150                 155                 160

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

                165                 170                 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala



            180                 185                 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val

        195                 200                 205

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

    210                 215                 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys

225                 230                 235                 240

Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val



                245                 250                 255

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr

            260                 265                 270

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu

        275                 280                 285

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

    290                 295                 300

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser



305                 310                 315                 320

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

                325                 330                 335

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile

            340                 345                 350

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

        355                 360                 365

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu



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

385   390   395   400

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

405   410   415

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg

420   425   430

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

435   440   445

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys

450   455   460

<210> 8

<211> 1999

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 8

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tcctgcaagg cttctggtta ttcattcact gactacatca tactctgggt gaagcagaac    180
catggaaaga gccttgagtg gattggacat attgatcctt actatggtag ttctaactac    240
aatctgaaat tcaagggcaa ggccacattg actgtagaca aatcttccag cacagcctac    300
atgcagctca acagtctgac atctgaggac tctgcagtct attactgtgg aagatctaag    360
agggactact ttgactactg gggccaaggc accactctca cagtttcctc agcctccacc    420
aagggcccat ccgtcttccc cctggcgccc tgctccagga gcacctccga gagcacagcc    480
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca    540
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac    600
tccctcagca gcgtggtgac cgtgccctcc agcaacttcg gcacccagac ctacacctgc    660
aacgtagatc acaagcccag caacaccaag gtggacaaga cagttggtga gaggccagct    720
cagggaggga gggtgtctgc tggaagccag gctcagccct cctgcctgga cgcaccccgg    780
ctgtgcagcc ccagcccagg gcagcaaggc aggccccatc tgtctcctca cccggaggcc    840
tctgcccgcc ccactcatgc tcagggagag ggtcttctgg ctttttccac caggctccag    900
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gcaggcacag gctgggtgcc cctaccccag gcccttcaca cacaggggca ggtgcttggc 960
tcagacctgc caaaagccat atccgggagg accctgcccc tgacctaagc cgaccccaaa 1020

ggccaaactg tccactccct cagctcggac accttctctc ctcccagatc cgagtaactc 1080
ccaatcttct ctctgcagag cgcaaatgtt gtgtcgagtg cccaccgtgc ccaggtaagc 1140
cagcccaggc ctcgccctcc agctcaaggc gggacaggtg ccctagagta gcctgcatcc 1200
agggacaggc cccagctggg tgctgacacg tccacctcca tctcttcctc agcaccacct 1260
gtggcaggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 1320
cggacccctg aggtcacgtg cgtggtggtg gacgtgagcc aggaagaccc cgaggtccag 1380
ttcaactggt acgtggatgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1440

cagttcaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1500
aacggcaagg agtacaagtg caaggtctcc aacaaaggcc tcccgtcctc catcgagaaa 1560
accatctcca aagccaaagg tgggacccac ggggtgcgag ggccacatgg acagaggtca 1620
gctcggccca ccctctgccc tgggagtgac cgctgtgcca acctctgtcc ctacagggca 1680
gccccgagag ccacaggtgt acaccctgcc cccatcccag gaggagatga ccaagaacca 1740
ggtcagcctg acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga 1800
gagcaatggg cagccggaga acaactacaa gaccacgcct cccgtgctgg actccgacgg 1860

ctccttcttc ctctacagca ggctaaccgt ggacaagagc aggtggcagg aggggaatgt 1920
cttctcatgc tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc 1980
cctgtctctg ggtaaatga 1999
<210> 9
<211> 337
<212> PRT
<213> Artificial Sequence
<220><223> Description of Artificial Sequence: Synthetic
polypeptide
<400> 9
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15
Val His Ser Leu Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val

20 25 30
Lys Pro Gly Ala Ser Leu Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser

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        35                  40                  45
Phe Thr Asp Tyr Ile Ile Leu Trp Val Lys Gln Asn His Gly Lys Ser
    50                  55                  60
Leu Glu Trp Ile Gly His Ile Asp Pro Tyr Tyr Gly Ser Ser Asn Tyr
65                  70                  75                  80
Asn Leu Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser

                85                  90                  95
Ser Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala
            100                 105                 110
Val Tyr Tyr Cys Gly Arg Ser Lys Arg Asp Tyr Phe Asp Tyr Trp Gly
        115                 120                 125
Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
    130                 135                 140
Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala

145                 150                 155                 160
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205
Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His

    210                 215                 220
Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
225                 230                 235                 240
Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
                245                 250                 255
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            260                 265                 270
Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu

        275                 280                 285
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Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    290                 295                 300
Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
305                 310                 315                 320
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                325                 330                 335
Cys


<210> 10
<211> 1600
<212> DNA


<213> Artificial Sequence
<220><223> Description of Artificial Sequence: Synthetic
      polynucleotide
<220><221> CDS
<222> (79)..(783)
<220><221> CDS
<222> (1176)..(1211)
<400> 10
gctgacagac taacagactg ttcctttcca tgggtctttt ctgcagtcac cgtccttgac     60
acgaggcgcg ccgccacc atg gga tgg agc tgt atc atc ctc ttc ttg gta      111
                    Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val
                    1               5                   10
gca aca gct aca ggt gtc cac tcc ctc gag gtc cag ctg caa cag tct      159

Ala Thr Ala Thr Gly Val His Ser Leu Glu Val Gln Leu Gln Gln Ser
            15                  20                  25
gga cct gag ctg gtg aag cct ggg gct tca ctg aag atg tcc tgc aag      207
Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Leu Lys Met Ser Cys Lys
        30                  35                  40
gct tct ggt tat tca ttc act gac tac atc ata ctc tgg gtg aag cag      255
Ala Ser Gly Tyr Ser Phe Thr Asp Tyr Ile Ile Leu Trp Val Lys Gln


    45                  50                  55
```

```
aac cat gga aag agc ctt gag tgg att gga cat att gat cct tac tat      303
Asn His Gly Lys Ser Leu Glu Trp Ile Gly His Ile Asp Pro Tyr Tyr
60                  65                  70                  75
ggt agt tct aac tac aat ctg aaa ttc aag ggc aag gcc aca ttg act      351
Gly Ser Ser Asn Tyr Asn Leu Lys Phe Lys Gly Lys Ala Thr Leu Thr
                80                  85                  90

gta gac aaa tct tcc agc aca gcc tac atg cag ctc aac agt ctg aca      399
Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr
            95                  100                 105
tct gag gac tct gca gtc tat tac tgt gga aga tct aag agg gac tac      447
Ser Glu Asp Ser Ala Val Tyr Tyr Cys Gly Arg Ser Lys Arg Asp Tyr
        110                 115                 120
ttt gac tac tgg ggc caa ggc acc act ctc aca gtt tcc tca gcc tcc      495

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser
    125                 130                 135
acc aag ggc cca tcc gtc ttc ccc ctg gcg ccc tgc tcc agg agc acc      543
Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
140                 145                 150                 155
tcc gag agc aca gcc gcc ctg ggc tgc ctg gtc aag gac tac ttc ccc      591
Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro

                160                 165                 170
gaa ccg gtg acg gtg tcg tgg aac tca ggc gcc ctg acc agc ggc gtg      639
Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            175                 180                 185
cac acc ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc ctc agc      687
His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        190                 195                 200

agc gtg gtg acc gtg ccc tcc agc aac ttc ggc acc cag acc tac acc      735
Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
    205                 210                 215
tgc aac gta gat cac aag ccc agc aac acc aag gtg gac aag aca gtt      783
```

```
Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
220                 225                 230                 235
ggtgagaggc cagctcaggg agggagggtg tctgctggaa gccaggctca gccctcctgc    843


ctggacgcac cccggctgtg cagccccagc ccagggcagc aaggcaggcc ccatctgtct    903
cctcacccgg aggcctctgc ccgccccact catgctcagg gagagggtct tctggctttt    963
tccaccaggc tccaggcagg cacaggctgg gtgcccctac cccaggccct tcacacacag   1023
gggcaggtgc ttggctcaga cctgccaaaa gccatatccg ggaggaccct gcccctgacc   1083
taagccgacc ccaaaggcca aactgtccac tccctcagct cggacacctt ctctcctccc   1143
agatccgagt aactcccaat cttctctctg ca gag cgc aaa tgt tgt gtc gag     1196
                                    Glu Arg Lys Cys Cys Val Glu


                                                    240
tgc cca ccg tgc cca ggtaagccag cccaggcctc gccctccagc tcaaggcggg     1251
Cys Pro Pro Cys Pro
        245
acaggtgccc tagagtagcc tgcatccagg gacaggcccc agctgggtgc tgacacgtcc   1311
acctccatct cttcctcagc accacctgtg gcaggaccgt cagtcttcct cttcccccca   1371
aaacccaagg acaccctcat gatctcccgg acccctgagg tcacgtgcgt ggtggtggac   1431


gtgagccagg aagaccccga ggtccagttc aactggtacg tggatggcgt ggaggtgcat   1491
aatgccaaga caaagccgcg ggaggagcag ttcaacagca cgtaccgtgt ggtcagcgtc   1551
ctcaccgtcc tgcaccagga ctggctgaac ggcaaggagt acaagtgca               1600
<210> 11
<211> 234
<212> PRT
<213> Artificial Sequence
<220><223> Description of Artificial Sequence: Synthetic
      polypeptide
<400> 11
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15
Val His Ser Arg Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Tyr


            20                  25                  30
```

Ala Ser Leu Gly Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp

35 40 45

Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro

50 55 60

Lys Thr Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser

65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser

85 90 95

Ser Leu Glu Tyr Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp

100 105 110

Glu Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg

115 120 125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln

130 135 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

145 150 155 160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser

165 170 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr

180 185 190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys

195 200 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro

210 215 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

225 230

<210> 12

<211> 705

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 12

atgggatgga gctgtatcat cctcttcttg gtagcaacag ctacaggtgt ccactctaga 60

gacatccaga tgacacagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 120

atcacttgca aggcgagtca ggacattaat agctatttaa gctggttcca gcagaaacca 180

gggaaatctc ctaagaccct gatctatcgt gcaaacagat tggtagatgg ggttccatca 240

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagtat 300

gaagatatgg gaatttatta ttgtctacag tatgatgagt ttccgtacac gttcggaggg 360

gggaccaagc tggaaataaa acggactgtg gctgcaccat ctgtcttcat cttcccgcca 420

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 480

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 540

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 600

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 660

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttaa 705

<210> 13

<211> 240

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 13

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly

1 5 10 15

Val His Ser Arg Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Tyr

20 25 30

Ala Ser Leu Gly Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp

35 40 45

Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro

50 55 60

Lys Thr Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser

65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser

                85   90   95

Ser Leu Glu Tyr Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp

            100   105   110

Glu Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg

        115   120   125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln

    130   135   140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

145   150   155   160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser

                165   170   175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr

            180   185   190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys

        195   200   205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro

    210   215   220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Ser Ala Ala Ala Ile His

225   230   235   240

<210> 14

<211> 738

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<220><221> CDS

<222> (16)..(735)

<400> 14

aagcttgccg ccacc atg gga tgg agc tgt atc atc ctc ttc ttg gta gca   51

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala

1   5   10

aca gct aca ggt gtc cac tct aga gac atc cag atg aca cag tct cca 99

Thr Ala Thr Gly Val His Ser Arg Asp Ile Gln Met Thr Gln Ser Pro

15 20 25

tct tcc atg tat gca tct cta gga gag aga gtc act atc act tgc aag 147

Ser Ser Met Tyr Ala Ser Leu Gly Glu Arg Val Thr Ile Thr Cys Lys

30 35 40

gcg agt cag gac att aat agc tat tta agc tgg ttc cag cag aaa cca 195

Ala Ser Gln Asp Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro

45 50 55 60

ggg aaa tct cct aag acc ctg atc tat cgt gca aac aga ttg gta gat 243

Gly Lys Ser Pro Lys Thr Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp

65 70 75

ggg gtt cca tca agg ttc agt ggc agt gga tct ggg caa gat tat tct 291

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser

80 85 90

ctc acc atc agc agc ctg gag tat gaa gat atg gga att tat tat tgt 339

Leu Thr Ile Ser Ser Leu Glu Tyr Glu Asp Met Gly Ile Tyr Tyr Cys

95 100 105

cta cag tat gat gag ttt ccg tac acg ttc gga ggg ggg acc aag ctg 387

Leu Gln Tyr Asp Glu Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu

110 115 120

gaa ata aaa cgg act gtg gct gca cca tct gtc ttc atc ttc ccg cca 435

Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro

125 130 135 140

tct gat gag cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg 483

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu

145 150 155

aat aac ttc tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac 531

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn

160 165 170

gcc ctc caa tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc 579

```
Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser

        175                 180                 185

aag gac agc acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca      627

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala


    190                 195                 200

gac tac gag aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc      675

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly

205                 210                 215                 220

ctg agc tcg ccc gtc aca aag agc ttc aac agg gga gag tgt tca gcg      723

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Ser Ala

                225                 230                 235


gcc gca att cat tga                                                  738

Ala Ala Ile His

            240
```

<210> 15

<211> 466

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 15

```
Met Gly Trp Ser Arg Ile Phe Leu Phe Leu Leu Ser Ile Ile Ala Gly

1               5                   10                  15

Val His Cys Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys


            20                  25                  30

Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe

        35                  40                  45

Thr Asp Tyr Ile Ile Leu Trp Val Arg Gln Asn Pro Gly Lys Gly Leu

    50                  55                  60

Glu Trp Ile Gly His Ile Asp Pro Tyr Tyr Gly Ser Ser Asn Tyr Asn

65                  70                  75                  80
```

```
Leu Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Gln Ser Thr Thr


                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val

            100                 105                 110

Tyr Tyr Cys Gly Arg Ser Lys Arg Asp Tyr Phe Asp Tyr Trp Gly Gln

        115                 120                 125

Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val

    130                 135                 140

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala


145                 150                 155                 160

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser

                165                 170                 175

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val

            180                 185                 190

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro

        195                 200                 205

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys


    210                 215                 220

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp

225                 230                 235                 240

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile

            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu


        275                 280                 285

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His

    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg

305                 310                 315                 320

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
```

325 330 335

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

340 345 350

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

355 360 365

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu

370 375 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

385 390 395 400

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

405 410 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp

420 425 430

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

435 440 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro

450 455 460

Gly Lys

465

<210> 16

<211> 1401

<212

> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 16

atgggatgga gccggatctt tctcttcctc ctgtcaataa ttgcaggtgt ccattgccag 60

gtccagctgc aacagtctgg atctgagctg aagaagcctg gggcttcagt gaagatctcc 120

tgcaaggctt ctggttattc attcactgac tacatcatac tctgggtgag gcagaaccct 180

ggaaagggcc ttgagtggat tggacatatt gatccttact atggtagttc taactacaat 240

ctgaaattca agggcagagt gacaatcacc gccgaccagt ctaccaccac agcctacatg 300 gagctctcca gtctgagatc tgaggacact gcagtctatt actgtggaag atctaagagg 360

gactactttg actactgggg ccaaggcacc actctcacag tttcctcagc ctccaccaag 420

ggcccatcgg tcttcccgct agcaccctcc tccaagagca cctctggggg cacagcggcc 480

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 540

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 600

ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 660

gtgaatcaca agcccagcaa caccaaggtg gacaagagag ttgagcccaa atcttgtgac 720

aaaactcaca catgcccacc gtgcccagca cctgaactcc tggggggacc gtcagtcttc 780

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc 840

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 900

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt 960

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 1020

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1080

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1140

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1200

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1260

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1320

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1380

tccctgtctc cgggtaaatg a 1401

<210> 17

<211> 1402

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic
polynucleotide

<220><221> CDS

<222> (2)..(1399)

<400> 17

c atg gga tgg agc cgg atc ttt ctc ttc ctc ctg tca ata att gca ggt 49

Met Gly Trp Ser Arg Ile Phe Leu Phe Leu Leu Ser Ile Ile Ala Gly

1 5 10 15

```
gtc cat tgc cag gtc cag ctg caa cag tct gga tct gag ctg aag aag       97
Val His Cys Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys
            20                  25                  30
cct ggg gct tca gtg aag atc tcc tgc aag gct tct ggt tat tca ttc      145
Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe


        35                  40                  45
act gac tac atc ata ctc tgg gtg agg cag aac cct gga aag ggc ctt      193
Thr Asp Tyr Ile Ile Leu Trp Val Arg Gln Asn Pro Gly Lys Gly Leu
    50                  55                  60
gag tgg att gga cat att gat cct tac tat ggt agt tct aac tac aat      241
Glu Trp Ile Gly His Ile Asp Pro Tyr Tyr Gly Ser Ser Asn Tyr Asn
65                  70                  75                  80


ctg aaa ttc aag ggc aga gtg aca atc acc gcc gac cag tct acc acc      289
Leu Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Gln Ser Thr Thr
                85                  90                  95
aca gcc tac atg gag ctc tcc agt ctg aga tct gag gac act gca gtc      337
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110
tat tac tgt gga aga tct aag agg gac tac ttt gac tac tgg ggc caa      385


Tyr Tyr Cys Gly Arg Ser Lys Arg Asp Tyr Phe Asp Tyr Trp Gly Gln
        115                 120                 125
ggc acc act ctc aca gtt tcc tca gcc tcc acc aag ggc cca tcg gtc      433
Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
    130                 135                 140
ttc ccg cta gca ccc tcc tcc aag agc acc tct ggg ggc aca gcg gcc      481
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala


145                 150                 155                 160
ctg ggc tgc ctg gtc aag gac tac ttc ccc gaa ccg gtg acg gtg tcg      529
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                165                 170                 175
tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc ccg gct gtc      577
```

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


cta cag tcc tca gga ctc tac tcc ctc agc agc gtg gtg acc gtg ccc      625
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
        195                 200                 205
tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg aat cac aag      673
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
    210                 215                 220
ccc agc aac acc aag gtg gac aag aga gtt gag ccc aaa tct tgt gac      721


Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
225                 230                 235                 240
aaa act cac aca tgc cca ccg tgc cca gca cct gaa ctc ctg ggg gga      769
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
                245                 250                 255
ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc      817
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile


            260                 265                 270
tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc cac gaa      865
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285
gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag gtg cat      913
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300


aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg tac cgt      961
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
305                 310                 315                 320
gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat ggc aag     1009
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335
```

gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc atc gag 1057

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

340 345 350

aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag gtg tac 1105

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

355 360 365

acc ctg ccc cca tcc cgg gag gag atg acc aag aac cag gtc agc ctg 1153

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu

370 375 380

acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg gag tgg 1201

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

385 390 395 400

gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct ccc gtg 1249

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

405 410 415

ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc gtg gac 1297

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp

420 425 430

aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat 1345

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

435 440 445

gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg tct ccg 1393

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro

450 455 460

ggt aaa tga 1402

Gly Lys

465

<210> 18

<211> 236

<212> PRT

<213> Artificial Sequence

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<220><223> Description of Artificial Sequence: Synthetic
      polypeptide


<400> 18
Met Asp Met Arg Val Ser Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15
Leu Ser Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30
Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
        35                  40                  45
Gln Asp Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys
    50                  55                  60


Ala Pro Lys Leu Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp Gly Val
65                  70                  75                  80
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
                85                  90                  95
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln
            100                 105                 110
Tyr Asp Glu Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
        115                 120                 125


Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190


Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220
```

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

225   230   235

<210> 19

<211> 711

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<

400> 19

atggacatga gggtctctgc tcagctcctg gggctcctgc tgctctggct ctcaggggcc 60

aggtgtgaca tccagatgac acagtctcca tcttccctgt ctgcatctat aggagacaga 120

gtcactatca cttgcaaggc gagtcaggac attaatagct atttaagctg gttccagcag 180

aaaccaggga aagctcctaa gctgctgatc tatcgtgcaa acagattggt agatggggtt 240

ccatcaaggt tcagtggcag tggatctggg acagattata ctctcaccat cagcagcctg 300

cagcctgaag atttcgcagt ttattattgt ctacagtatg atgagtttcc gtacacgttc 360

ggaggggggа ccaagctgga aataaaacgt acggtggctg caccatctgt cttcatcttc 420

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 480

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgtta g 711

<210> 20

<211> 765

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<220><221> CDS

<222> (55)..(762)

<400> 20

tttccatggg tcttttctgc agtcaccgtc cttgacacga agcttgccgc cacc atg 57

Met

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                                                            1
gac atg agg gtc tct gct cag ctc ctg ggg ctc ctg ctg ctc tgg ctc      105
Asp Met Arg Val Ser Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu
            5                   10                  15
tca ggg gcc agg tgt gac atc cag atg aca cag tct cca tct tcc ctg      153

Ser Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
        20                  25                  30
tct gca tct ata gga gac aga gtc act atc act tgc aag gcg agt cag      201
Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln
    35                  40                  45
gac att aat agc tat tta agc tgg ttc cag cag aaa cca ggg aaa gct      249
Asp Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ala

50                  55                  60                  65
cct aag ctg ctg atc tat cgt gca aac aga ttg gta gat ggg gtt cca      297
Pro Lys Leu Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro
                70                  75                  80
tca agg ttc agt ggc agt gga tct ggg aca gat tat act ctc acc atc      345
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
            85                  90                  95

agc agc ctg cag cct gaa gat ttc gca gtt tat tat tgt cta cag tat      393
Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Tyr
        100                 105                 110
gat gag ttt ccg tac acg ttc gga ggg ggg acc aag ctg gaa ata aaa      441
Asp Glu Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
    115                 120                 125
cgt acg gtg gct gca cca tct gtc ttc atc ttc ccg cca tct gat gag      489

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130                 135                 140                 145
cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc      537
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
                150                 155                 160
```

tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa 585

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln

165 170 175

tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc aag gac agc 633

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser

180 185 190

acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca gac tac gag 681

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu

195 200 205

aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg 729

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser

210 215 220 225

ccc gtc aca aag agc ttc aac agg gga gag tgt tag 765

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

230 235

<210> 21

<211> 462

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 21

Met Gly Trp Ser Arg Ile Phe Leu Phe Leu Leu Ser Ile Ile Ala Gly

1 5 10 15

Val His Cys Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Lys Lys

20 25 30

Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe

35 40 45

Thr Asp Tyr Ile Ile Leu Trp Val Arg Gln Asn Pro Gly Lys Gly Leu

50 55 60

Glu Trp Ile Gly His Ile Asp Pro Tyr Tyr Gly Ser Ser Asn Tyr Asn

```
65                  70                  75                  80
Leu Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Gln Ser Thr Thr
                85                  90                  95
Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110
Tyr Tyr Cys Gly Arg Ser Lys Arg Asp Tyr Phe Asp Tyr Trp Gly Gln


        115                 120                 125
Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
    130                 135                 140
Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
145                 150                 155                 160
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                165                 170                 175
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val


            180                 185                 190
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
        195                 200                 205
Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
    210                 215                 220
Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
225                 230                 235                 240
Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe


                245                 250                 255
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270
Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
        275                 280                 285
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val


305                 310                 315                 320
```

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

                325   330   335

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser

            340   345   350

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

        355   360   365

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val

    370   375   380

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

385   390   395   400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

                405   410   415

Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp

            420   425   430

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His

        435   440   445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys

    450   455   460

<210> 22

<211> 2002

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic
      polynucleotide

<400> 22

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gaggtccagc tgcaacagtc tggacctgag ctggtgaagc ctggggcttc actgaagatg   120

tcctgcaagg cttctggtta ttcattcact gactacatca tactctgggt gaagcagaac   180

catggaaaga gccttgagtg gattggacat attgatcctt actatggtag ttctaactac   240

aatctgaaat tcaagggcaa ggccacattg actgtagaca aatcttccag cacagcctac   300

atgcagctca acagtctgac atctgaggac tctgcagtct attactgtgg aagatctaag   360

agggactact ttgactactg gggccaaggc accactctca cagtttcctc agcctccacc   420

aagggcccat ccgtcttccc cctggcgccc tgctccagga gcacctccga gagcacagcc 480
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 540
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 600

tccctcagca gcgtggtgac cgtgccctcc agcaacttcg gcacccagac ctacacctgc 660
aacgtagatc acaagcccag caacaccaag gtggacaaga cagttggtga gaggccagct 720
cagggaggga gggtgtctgc tggaagccag gctcagccct cctgcctgga cgcaccccgg 780
ctgtgcagcc ccagcccagg gcagcaaggc aggccccatc tgtctcctca cccggaggcc 840
tctgcccgcc ccactcatgc tcagggagag ggtcttctgg ctttttccac caggctccag 900
gcaggcacag gctgggtgcc cctaccccag gcccttcaca cacaggggca ggtgcttggc 960
tcagacctgc caaaagccat atccgggagg accctgcccc tgacctaagc cgaccccaaa 1020

ggccaaactg tccactccct cagctcggac accttctctc ctcccagatc cgagtaactc 1080
ccaatcttct ctctgcagag cgcaaatgtt gtgtcgagtg cccaccgtgc ccaggtaagc 1140
cagcccaggc ctcgccctcc agctcaaggc gggacaggtg ccctagagta gcctgcatcc 1200
agggacaggc cccagctggg tgctgacacg tccacctcca tctcttcctc agcaccacct 1260
gtggcaggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 1320
cggacccctg aggtcacgtg cgtggtggtg gacgtgagcc aggaagaccc cgaggtccag 1380
ttcaactggt acgtggatgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 1440

cagttcaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1500
aacggcaagg agtacaagtg caaggtctcc aacaaaggcc tcccgtcctc catcgagaaa 1560
accatctcca aagccaaagg tgggacccac ggggtgcgag ggccacatgg acagaggtca 1620
gctcggccca ccctctgccc tgggagtgac cgctgtgcca acctctgtcc ctacagggca 1680
gccccgagag ccacaggtgt acaccctgcc cccatcccag gaggagatga ccaagaacca 1740
ggtcagcctg acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga 1800
gagcaatggg cagccggaga acaactacaa gaccacgcct cccgtgctgg actccgacgg 1860

ctccttcttc ctctacagca ggctaaccgt ggacaagagc aggtggcagg aggggaatgt 1920
cttctcatgc tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc 1980
cctgtctctg ggtaaatgat ga 2002
<210> 23
<211> 2163
<212> DNA
<213> Artificial Sequence

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<220><223> Description of Artificial Sequence: Synthetic
      polynucleotide
<220><221> CDS
<222> (94)..(798)
<220><221> CDS
<222> (1191)..(1226)
<220><221> CDS
<222> (1345)..(1671)
<220><221> CDS
<222> (1769)..(2089)


<400> 23
ccaccagaca taatagctga cagactaaca gactgttcct ttccatgggt cttttctgca     60
gtcaccgtcc ttgacacgaa gcttgccgcc acc atg gga tgg agc tgt atc atc     114
                                     Met Gly Trp Ser Cys Ile Ile
                                     1               5
ctc ttc ttg gta gca aca gct aca ggt gtc cac tcc ctc gag gtc cag      162
Leu Phe Leu Val Ala Thr Ala Thr Gly Val His Ser Leu Glu Val Gln
        10                  15                  20


ctg caa cag tct gga cct gag ctg gtg aag cct ggg gct tca ctg aag      210
Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Leu Lys
    25                  30                  35
atg tcc tgc aag gct tct ggt tat tca ttc act gac tac atc ata ctc      258
Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr Ile Ile Leu
40                  45                  50                  55
tgg gtg aag cag aac cat gga aag agc ctt gag tgg att gga cat att      306


Trp Val Lys Gln Asn His Gly Lys Ser Leu Glu Trp Ile Gly His Ile
                60                  65                  70
gat cct tac tat ggt agt tct aac tac aat ctg aaa ttc aag ggc aag      354
Asp Pro Tyr Tyr Gly Ser Ser Asn Tyr Asn Leu Lys Phe Lys Gly Lys
            75                  80                  85
gcc aca ttg act gta gac aaa tct tcc agc aca gcc tac atg cag ctc      402
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```
Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu


        90                  95                  100

aac agt ctg aca tct gag gac tct gca gtc tat tac tgt gga aga tct      450

Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Gly Arg Ser

    105                 110                 115

aag agg gac tac ttt gac tac tgg ggc caa ggc acc act ctc aca gtt      498

Lys Arg Asp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val

120                 125                 130                 135


tcc tca gcc tcc acc aag ggc cca tcc gtc ttc ccc ctg gcg ccc tgc      546

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys

                140                 145                 150

tcc agg agc acc tcc gag agc aca gcc gcc ctg ggc tgc ctg gtc aag      594

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys

            155                 160                 165

gac tac ttc ccc gaa ccg gtg acg gtg tcg tgg aac tca ggc gcc ctg      642


Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu

        170                 175                 180

acc agc ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctc      690

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu

    185                 190                 195

tac tcc ctc agc agc gtg gtg acc gtg ccc tcc agc aac ttc ggc acc      738

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr


200                 205                 210                 215

cag acc tac acc tgc aac gta gat cac aag ccc agc aac acc aag gtg      786

Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val

                220                 225                 230

gac aag aca gtt ggtgagaggc cagctcaggg agggagggtg tctgctggaa          838

Asp Lys Thr Val

            235
```

```
gccaggctca gccctcctgc ctggacgcac cccggctgtg cagccccagc ccagggcagc    898
aaggcaggcc ccatctgtct cctcacccgg aggcctctgc ccgccccact catgctcagg    958
gagagggtct tctggctttt tccaccaggc tccaggcagg cacaggctgg gtgcccctac   1018
cccaggccct tcacacacag gggcaggtgc ttggctcaga cctgccaaaa gccatatccg   1078
ggaggaccct gcccctgacc taagccgacc ccaaaggcca aactgtccac tccctcagct   1138
cggacacctt ctctcctccc agatccgagt aactcccaat cttctctctg ca gag cgc   1196
                                                          Glu Arg



aaa tgt tgt gtc gag tgc cca ccg tgc cca ggtaagccag cccaggcctc       1246
Lys Cys Cys Val Glu Cys Pro Pro Cys Pro
        240                 245
gccctccagc tcaaggcggg acaggtgccc tagagtagcc tgcatccagg gacaggcccc   1306
agctgggtgc tgacacgtcc acctccatct cttcctca gca cca cct gtg gca gga   1362
                                          Ala Pro Pro Val Ala Gly


                                                  250
ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc atg atc     1410
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    255                 260                 265
tcc cgg acc cct gag gtc acg tgc gtg gtg gtg gac gtg agc cag gaa     1458
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
270                 275                 280                 285


gac ccc gag gtc cag ttc aac tgg tac gtg gat ggc gtg gag gtg cat     1506
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                290                 295                 300
aat gcc aag aca aag ccg cgg gag gag cag ttc aac agc acg tac cgt     1554
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
            305                 310                 315
gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aac ggc aag     1602


Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        320                 325                 330
gag tac aag tgc aag gtc tcc aac aaa ggc ctc ccg tcc tcc atc gag     1650
```

```
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
    335                 340                 345
aaa acc atc tcc aaa gcc aaa ggtgggaccc acggggtgcg agggccacat        1701
Lys Thr Ile Ser Lys Ala Lys


350                 355
ggacagaggt cagctcggcc caccctctgc cctgggagtg accgctgtgc caacctctgt   1761
ccctaca ggg cag ccc cga gag cca cag gtg tac acc ctg ccc cca tcc     1810
        Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
                    360                 365                 370
cag gag gag atg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa     1858
Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys


                375                 380                 385
ggc ttc tac ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag     1906
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
            390                 395                 400
ccg gag aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc     1954
Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
        405                 410                 415


tcc ttc ttc ctc tac agc agg cta acc gtg gac aag agc agg tgg cag     2002
Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
    420                 425                 430
gag ggg aat gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac     2050
Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
435                 440                 445                 450
cac tac aca cag aag agc ctc tcc ctg tct ctg ggt aaa tgatgagaat      2099


His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
                455                 460
tcattgatca taatcagcca taccacattt gtagaggttt tacttgcttt aaaaaacctc   2159
ccac                                                                2163
<210> 24
<211> 236
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<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 24

Met Asp Met Arg Val Ser Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp

1 5 10 15

Leu Ser Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser

20 25 30

Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser

35 40 45

Gln Asp Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys

50 55 60

Ala Pro Lys Leu Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp Gly Val

65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr

85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln

100 105 110

Tyr Asp Glu Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile

115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp

130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn

145 150 155 160

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

165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp

180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr

195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser

210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

225 230 235

<210> 25

<211> 711

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 25

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atggacatga gggtctctgc tcagctcctg gggctcctgc tgctctggct ctcaggggcc     60


aggtgtgaca tccagatgac acagtctcca tcttccctgt ctgcatctat aggagacaga    120

gtcactatca cttgcaaggc gagtcaggac attaatagct atttaagctg gttccagcag    180

aaaccaggga aagctcctaa gctgctgatc tatcgtgcaa acagattggt agatggggtt    240

ccatcaaggt tcagtggcag tggatctggg acagattata ctctcaccat cagcagcctg    300

cagcctgaag atttcgcagt ttattattgt ctacagtatg atgagtttcc gtacacgttc    360

ggagggggga ccaagctgga aataaaacgt acggtggctg caccatctgt cttcatcttc    420

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac    480


ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac    540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc    600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat    660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgtta g             711
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<210> 26

<211> 765

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<220><221> CDS

<222> (55)..(762)

<400> 26

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tttccatggg tcttttctgc agtcaccgtc cttgacacga agcttgccgc cacc atg       57


                                                            Met

                                                            1

gac atg agg gtc tct gct cag ctc ctg ggg ctc ctg ctg ctc tgg ctc      105

Asp Met Arg Val Ser Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu

            5                   10                  15

tca ggg gcc agg tgt gac atc cag atg aca cag tct cca tct tcc ctg      153

Ser Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu


        20                  25                  30

tct gca tct ata gga gac aga gtc act atc act tgc aag gcg agt cag      201

Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln

    35                  40                  45

gac att aat agc tat tta agc tgg ttc cag cag aaa cca ggg aaa gct      249

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

50                  55                  60                  65


cct aag ctg ctg atc tat cgt gca aac aga ttg gta gat ggg gtt cca      297

Pro Lys Leu Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro

                70                  75                  80

tca agg ttc agt ggc agt gga tct ggg aca gat tat act ctc acc atc      345

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile

            85                  90                  95

agc agc ctg cag cct gaa gat ttc gca gtt tat tat tgt cta cag tat      393


Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Tyr

        100                 105                 110

gat gag ttt ccg tac acg ttc gga ggg ggg acc aag ctg gaa ata aaa      441

Asp Glu Phe Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys

    115                 120                 125

cgt acg gtg gct gca cca tct gtc ttc atc ttc ccg cca tct gat gag      489

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
```

```
130                 135                 140                 145

cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc      537

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe

                150                 155                 160

tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa      585

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln

            165                 170                 175


tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc aag gac agc      633

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser

        180                 185                 190

acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca gac tac gag      681

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu

    195                 200                 205

aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg      729


Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser

210                 215                 220                 225

ccc gtc aca aag agc ttc aac agg gga gag tgt tag                      765

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

                230                 235
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<210> 27

<211> 448

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 27

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Arg

1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr

            20                  25                  30

Tyr Met Ala Trp Val Arg Gln Ala Pro Lys Lys Gly Leu Glu Trp Val

        35                  40                  45
```

```
Ala Ser Ile Gly Tyr Glu Gly Thr Ser Thr Tyr Tyr Gly Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95
Thr Arg Leu Glu Leu Ala Gly Val Met Asp Ala Trp Gly Gln Gly Ala
            100                 105                 110
Ser Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro
        115                 120                 125


Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly
    130                 135                 140
Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn
145                 150                 155                 160
Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175
Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr
            180                 185                 190


Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser
        195                 200                 205
Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro
    210                 215                 220
Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Glu Gly Gly Pro Ser
225                 230                 235                 240
Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu
                245                 250                 255


Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro
            260                 265                 270
Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala
        275                 280                 285
Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val
```

    290   295   300

Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Ala Phe

305   310   315   320

Ala Cys Ala Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr

                325   330   335

Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu

            340   345   350

Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys

        355   360   365

Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn

    370   375   380

Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp

385   390   395   400

Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys

                405   410   415

Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly

            420   425   430

Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys

        435   440   445

<210> 28

<211> 448

<212> PRT

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

      polypeptide

<400> 28

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Arg

1   5   10   15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr

            20   25   30

Tyr Met Ala Trp Val Arg Gln Ala Pro Lys Lys Gly Leu Glu Trp Val

```
        35                  40                  45


Ala Ser Ile Gly Tyr Glu Gly Thr Ser Thr Tyr Tyr Gly Asp Ser Val

    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr

65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys

                85                  90                  95

Thr Arg Leu Glu Leu Ala Gly Val Met Asp Ala Trp Gly Gln Gly Ala

            100                 105                 110


Ser Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro

        115                 120                 125

Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly

    130                 135                 140

Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn

145                 150                 155                 160

Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln

                165                 170                 175


Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr

            180                 185                 190

Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser

        195                 200                 205

Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro

    210                 215                 220

Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser

225                 230                 235                 240


Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu

                245                 250                 255

Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro

            260                 265                 270

Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala

        275                 280                 285
```

```
Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val
    290                 295                 300


Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe
305                 310                 315                 320
Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr
                325                 330                 335
Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu
            340                 345                 350
Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys
        355                 360                 365


Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn
    370                 375                 380
Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp
385                 390                 395                 400
Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys
                405                 410                 415
Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly
            420                 425                 430


Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
        435                 440                 445
```