





[ : Bouding M - L and Boulanger P: Assembly of Adenovirus Penton Base and Fiber, Virology, 116: 589 - 604, 1982].

Ad 가  
C - 가 [ : Michael SI, Hoy JS, Curie DT and Engles JT: Addition of a short peptide ligand to the adenovirus fiber protein. Gene Therapy 2: 660 - 8, 1995.] " "

. Ad FLAG - , Ad  
Ad FLAG

2 - [ : Wickham T J, Segal DM, Roelvink PW, Carrion ME, Lizonova A, Lee GM and Kovesdi I: Targeted Adenovirus Gene Transfer to Endothelial and Smooth Muscle Cells by Using Bispecific Antibodies. J. Virol., 70: 6831 - 6838, 1996.]. Ad

Ad가 [ : Trapnell BC and Gorziglia: Gene therapy using adenoviral vectors, Current Opinion in Biotechnology, 5: 617 - 625, 1994.], Ad -

가

가

가

가

가

DNA

가

:

a) (Spe1 ) 9kb ,

b) Sac1 Kpn1 3kb 가 ,

c) Nde1 Mun1 Xho1 S

EQ ID NO: 13 ;

d) c) Nde1 Xho1 ;  
 e) Nhe1 9kb d) ;  
 f) e) 9kb Spe1 27k  
 b) 9kb .

1: .  
 2: .  
 3: Ad .  
 4a: , CPE/ Ad  
 4b: , CPE/ Ad  
 Ad  
 가 , RGD , Fab ( 1) , T  
 가

(EGF), RGD, HLA - A1 MAGE - 1  
 T - (scTCR)[ : vd Bruggen P, Traversaari C, Chomez P, Lu  
 rquin D, De Plaen E, vd Eynde B, Knuth A and Boon T: A Gene encoding an Antigen Recognized by Cytoly  
 tic T Lymphocytes on a Human Melanoma, Science 13 December 1991, 1643 - 1647.],  
 G250 (scFv)[ :  
 Oosterwijk E, Ruitter DJ, Hoedemaeker PhJ, et al: Monoclonal antibody G250 recognizes a determinant pre  
 sent in renal - cell carcinoma and absent from normal kidney. Int J Cancer 38: 489 - 94, 1986.]  
 G250 가 ( ).

Ad 가 , 가 Ad  
 가 [ : Miller R and Curiel DT: Towards the use of  
 replicative adenoviral vectors for cancer gene therapy, Gene Therapy 3: 557 - 559].

가

, 가  
 - 가 Ad Ad

가

N -

가

가

1  
SDS - PAGE

가

/

가

가

2A6.36

가

[ : Shin Hong J and En

gler JA: The amino terminus of the adenovirus fiber protein encodes the nuclear localization signal, *Virology* 185: 758 - 767, 1991],

PCR[ : Clackson T, Güssow D and Jones PT: General application of PCR to gene cloning and manipulation, in *PCR, A Practical Approach*, Eds McPherson MJ, Quirke P and Taylor GR, IRL Press, Oxford, p 187, 1992], PCR - PCR[ : Alvaro Ali S, Steinkasserer A: PCR - ligation - PCR Mutagenesis: A Protocol for Creating Gene Fusion and Mutations, *BioTechniques* 18: 746 - 750, 1995] (SOE)[ : Horton RM and Pease LR: Recombination and mutagenesis of DNA sequences using PCR, in McPherson MJ (ed), *Directed Mutagenesis*, IRL Press 1991, p 217.]

ABI (Perkin Elme  
r ABI Prism)

가

:

Ad

가

가 .

1:

TLWT

2가 : a)

b)

. 2가

" D" 36 " (Neck Region Peptide)" =

NRP( SEQ ID NO: 1)[ : Hoppe H - J, Barlow PN and Reid KBM: A parallel three stranded - helical bundle at the nucleation site of collagen triple - helix formation. FEBS Letters 344: 191 - 195 (1994).

] 1 4 가 31 aa " (Zipper)" = pII( SEQ

ID NO: 2)[ : Harbury PB, Tao Zhang, Kim PS and Alber T: A Switch Between Two - , Three - , and Four - Stranded Coiled Coils in GCN4 Leucine Zipper Mutants. Science 262: 1401 - 1407, 1993.]가 .

DNA

가

가 .

가

가 .

가

SEQ ID NO: 10 12

( 2 ).

SEQ ID NO: 14

A

가 4 1

TLWT

2 (turn)( b)

가

가

B

A

가 .

C

가 1  
가

가 17 21  
가

D

가 가  
가

Nhe1 Hpa1

D/

D

A B

D

D (D/ )

E

A

가

SEQ ID NO: 3,

SEQ ID NO: 4,

SEQ ID NO: 5,

SEQ ID NO: 6,

A

SEQ ID NO: 7, IgG3

SEQ ID NO: 8, Ad5

17

Sf9

Ad5 COS )

/ 4D2.5( Ad5 pSecTag ) 2A6.36(

1

가

I.

파이버 타입 A	검출항체			
	4D2	2A6	a-EGF	a-Ig a-Id
A1 RGD	+	+		
A1 EGF	+	+	+	
A1 G250 HK	+	+		+ +
A1 G250 KH	+	+		+ +
A1 G250 KHJCH2	+	+		+ +
A1 VaLVβCβ	+	+		
A7 RGD	+	+		
A7 EGF	+	+	+	
A7 G250 HK	+	+		+ +
A7 G250 KH	+	+		+ +
A7 G250 KHJCH2	+	+		+ +
A7 VaLVβCβ	+	+		
A7 IgG3 EGF	+	+	+	
A7 (Gly4Ser)4 G250VKVH	+	+		+ +
A22 EGF	+	+	+	
A22 RGD	+	+		
타입 B				
B (Gly4Ser)4 RGD	+	+		
타입 C				
C IgG3 EGF	+	+	+	
C (Gly4Ser)4-G250VKVH	+	+		+ +
타입 D				
N/D EGF	+	+	+	
N/D G250 HKCKγ	+	+		+ +
F2/D EGF	+	+	+	
F3/D EGF	+	+	+	
타입 D/Δ				
F2 D/Δ G250 HKCK	+	+	+	
F2 D/Δ G250 HKCKγ	+	+		+ +
F2 D/Δ EGF	+	+	+	
F3 D/Δ EGF	+	+	+	

1 :

2A6:

4D2:

a - EGF:

a - Id: G250

a - Ig:

C : MAGE1/HLA A1

T

. SEQ ID NO: 11.

CH2:

2

EGF:

G250:

H: G250 가 (SEQ ID NO: 15)

IgG3: IgG3 , SEQ ID NO: 7

J:

K: G250 가 (SEQ ID NO: 16)

RGD: - -

V : MAGE1/HLA A1 T 가 . SEQ ID NO: 10

V : MAGE1/HLA A1 T 가 . SEQ ID NO: 12

2:

( 2 3)

24

Sf9

가

2

가

Sf9

2

Sf9

파이버 감염 후에 핵 국부화를 나타낸 파이버-발현 Sf9 세포의 %

야생형	100
N/D EGF	100
A RGD	약 50
A7 RGD	약 100
A7 EGF	약 100
A7 scTCR	약 50
A7 G250 scFvs	0

COS

pcDNA 3.1

가

- T -

가

, , 가

( ) .

가

SV40

T -

(NLS) 가

SEQ ID

NO: 9 가 [ : Fisher - Fantuzzi L and Vesco C: Cell - Dependent Efficiency of Reiterated Nuclear Signals in a Mutant Simian Virus 40 Oncoprotein Targeted to the Nucleus. Mol Cell Biol, 8: 5495 - 5503, 1988]. NLS RGD 가 . NLS 가

NLS가

( 3 ).

3

COS

파이버	해 국부화
야생형	+
A VαLVβCβ	+
A VαLVβCβCκ	+
A RGD	-
A NLS RGD	+
A7 RGD	-
A7 NLS RGD	+
A22 RGD	-

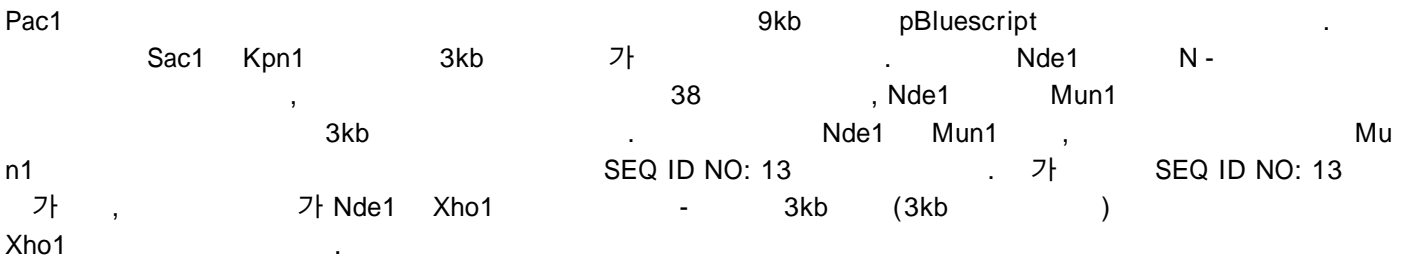
1 .

가 ( )  
NLS 가 .

3:

Ad ( 3 ).

Pac1 - Pac1 Ad5 pTG3602[ : Chartier C, Degryse E, Gantzer M, Dieterl A, Pavirani A and Mehtali M: Efficient generation of Recombinant Adenovirus Vectors by Homologous Recombination in Escherichia Coli, J Virol, 70: 4805 - 4810, 1996] . Spe1



PCR Hind III

Ad Pac1

4a 4b

가

가 가 [ : Miller N and Vile R: Targeted vectors for gene therapy. FASEB J, 9: 190 - 199, 1995].

가 -가

(trafficking)

가

scTCR 가 -가  
가

scAb

Ad -

가

Ad

I.

" "

II.  
it)

가  
가

(h

p53

eck)"

11 2

" - - (head - and - n  
(

)

(57)

1. , (shaft) (knob)  
가 가 , .
2. 1 , DNA .
3. 1 , 가 .
4. 1 , 가 .
5. 1 , 가 .
6. 4 , 가 Nhe1 Hpa1 .
7. 4 , 가 .
8. 4 , Hpa1 가 .
9. 1 , 가 가 /  
가 .
10. 9 , 가 SEQ ID NO: 3;  
A SEQ ID NO: 4; SEQ ID NO: 5;  
17 SEQ ID NO: 6; IgG3 SEQ ID NO: 7; Ad5  
SEQ ID NO: 8 .

11.

1 10 , 가

12.

11 , 가 Fab , T  
, RGD

13.

12 , SEQ ID NO: 10 SEQ ID NO: 12

14.

12 , SEQ ID NO: 15 가 SEQ ID NO: 16 가  
가 G250

15.

1 , 가 -

16.

15 , 가 가 D (neck) SEQ ID NO: 1  
1 4 가 31 " (Zipper)" SEQ ID NO: 2

17.

1 16 , (NLS)

18.

17 , NLS가 SV40 T NLS

19.

1 17 , 가 가 가

20.

19 ,

21.

20 , SEQ ID NO: 10 SEQ ID NO: 12

22.

1 21 ,

23.

I. a) (Spe1 ) 9 kb ,

b) Sac1 Kpn1 3 kb 가 ,

c) Nde1 Mun1 Xho1 SEQ ID NO: 13 ,

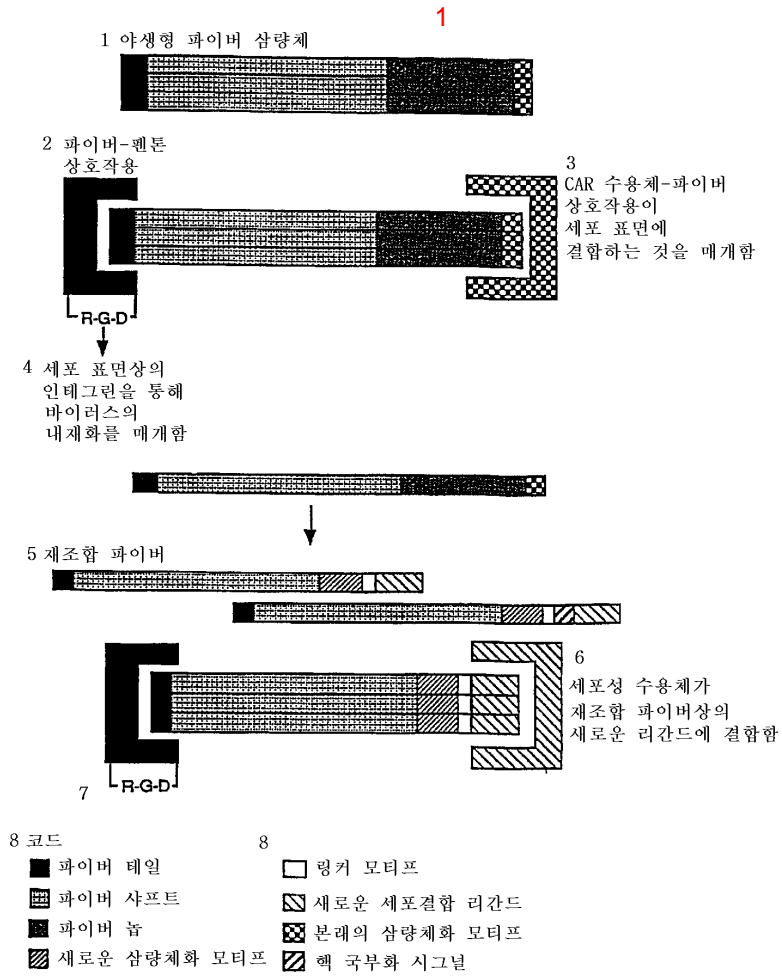
d) c) Nde1 Xho1 ,

e) Nhe1 9 kb d) ,

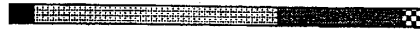
f) e) 9 kb Spe1 27 k  
b 9 kb

(rescue) ;

II. f) 가



야생형 파이버



타입 A



타입 A1. 샤프트 반복단위 1



타입 A7. 샤프트 반복단위 1-7



타입 B



타입 C



타입 D R1 R18-21



R 1-8 R18-21

타입 DΔ. R18-21가 결여된 변이체



타입 E. 위의 A, B 및 C 시트를 포함



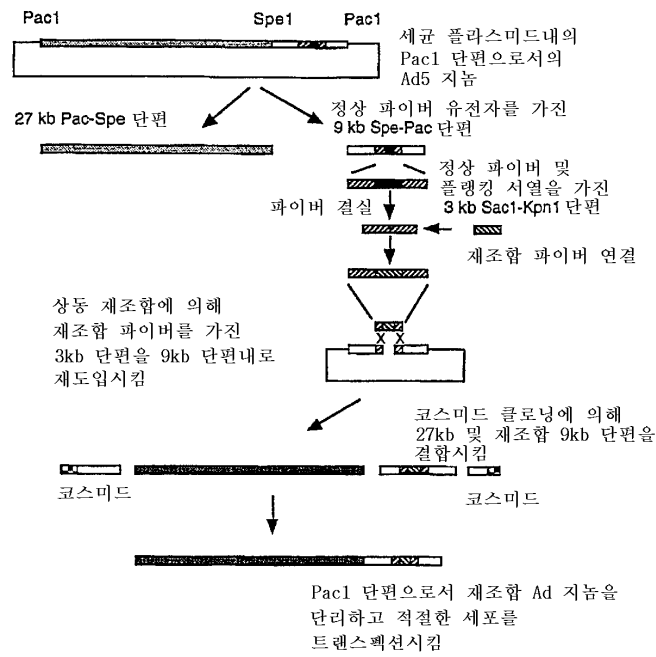
코드

-  파이버 테일
  -  파이버 샤프트
  -  파이버 늑
  -  새로운 삼량체화 모티프
  -  링커 모티프
  -  새로운 세포결합 리간드
  -  본래의 삼량체화 모티프
- R = 샤프트 반복단위

링커 모티프

- ASGGPE = 슈도모나스 외독소
- ASEGNSD = TPA
- ASTPEPDP = Ab 현저, 마우스
- SpA로부터의 AKKLNDACAPKSD
- TPLGDTTHTSG = 사람 IgG3로부터의 상단 현저 (GGGS)<sub>4</sub>

3



4a

타입 A

일자 트랜스팩션된 세포상의  
플라크 발생에 대해  
일(日)로 관찰한 시간

A1 늑	14
A7 늑	11-14
A1 RGD	23
A7 RGD	16
A7 NLS RGD	공지되지 않음
A1 EGF	불명확
A1 scFv	불명확
A1 scTCR	불명확
A7 scTCR	불명확
	야생형과 동일
	야생형과 동일
	야생형과 동일

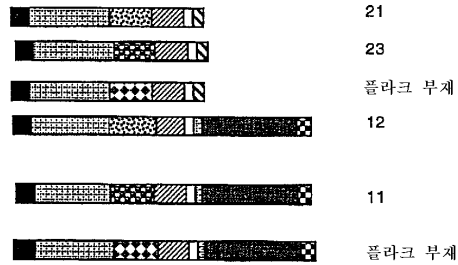
컬러 코드

■ 파이버 테일	□ 단일 사슬 항체
▨ 파이버 샤프트	▨ Vα
▩ 파이버 늑	▩ Vβ
▧ 새로운 삼량체화 모티프	▧ Cp
□ 링커 모티프	□ Ck
▨ EGF	▨ RGD
▩ 본래의 삼량체화 모티프	▩ 핵 국부화 시그널

4b

일차 트랜스팩션된 세포상의 플라크 발생에 대해 일(日)로 환산한 시간

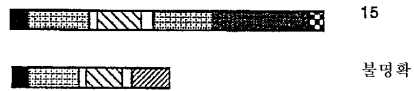
타입 B



타입 C



타입 D



코드

- 파이버 테일      (Gly4Ser)<sub>4</sub> 링커
- ▨ 파이버 샤프트      Ad5 파이버 샤프트의 반복단위 17로부터의 턴 b
- ▩ 파이버 늑      Ad5 파이버 샤프트의 반복단위 22로부터의 턴 b
- ▧ 새로운 삼량체화 모티프
- 링커 모티프
- ▨ EGF
- ▩ 본래의 삼량체화 모티프

Sequence listing

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 <302> A parallel three stranded  $\alpha$ -helical bundle at the nucleation site of collagen triple-helix formation  
 <303> FEBS Letters  
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 20 25 30  
 Glu Leu Phe Pro Asn Gly  
 35

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 <302> A switch between two-, three-, and four-stranded coiled coils  
 in GCN4 leucine zipper mutants  
 <303> Science  
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 <303> Proc Natl Acad Sci US  
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 Oi T  
 <302> Segmental flexibility and complement fixation of genetically  
 engineered chimeric human, rabbit and mouse antibodies  
 <303> EMBO Journal  
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 35 40 45  
 Arg Arg Asn Ser Phe Asp Glu Gln Asn Glu Ile Ser Gly Arg Tyr Ser  
 50 55 60 65  
 Trp Asn Phe Gln Lys Ser Thr Ser Ser Phe Asn Phe Thr Ile Thr Ala  
 70 75 80  
 Ser Gln Val Val Asp Ser Ala Val Tyr Phe Cys Ala Leu Gly Gly Val  
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 35 40 45  
 Val Asn Gly Lys Glu Val His Ser Gly Val Set Thr Asp Pro Gln Pro  
 50 55 60  
 Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser  
 65 70 75

Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe  
 80 85 90  
 Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr  
 95 100 105 110  
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 Arg Ala Asp Ala Ala Ala

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 35 40 45  
 Tyr Tyr Asn Gly Glu Glu Arg Ala Lys Gly Asn Ile Leu Glu Arg Phe  
 50 55 60 65  
 Ser Ala Gln Gln Phe Pro Asp Leu His Ser Glu Leu Asn Leu Ser Ser  
 70 75 80  
 Leu Glu Leu Gly Asp Ser Ala Leu Val Phe Cys Ala Ser Asn Ile Ala  
 85 90 95  
 Gly Gly Ser Tyr Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr Val  
 100 105 110

Leu

<210> 13  
 <211> 52  
 <212> DNA  
 <213> Artificial sequence  
 <223> Sequence replacing the fiber gene sequence which was deleted  
 between the Nde1 restriction site in the fiber tail and the Mun1  
 site which begins at base 38 after the stop codon in the fiber.  
 The sequence restores the Nde1 and Mun1 sites and the wild type  
 genome sequence between the fiber stop codon and the Mun1 site.  
 In addition the added sequence contains an Xho1 site allowing for  
 the ligation of recombinant fibers.  
 <400> 13

tatgcactcg agtaaagaat cgtttgtggt atgtttcaac gtgtttatattt tc

<210> 14  
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 <212> DNA  
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 <221> CDS  
 <222> 1-1746  
 <223> 1-129 Fiber tail  
 130-1200 Fiber shaft  
 1201-1746 Fiber knob

```

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Met Lys Arg Ala Arg Pro Ser Glu Asp Thr Phe Asn Pro Val Tyr Pro
1          5          10          15
tat gac acg gaa acc ggt cct cca act gtg cct ttt ctt act cct ccc      96
Tyr Asp Thr Glu Thr Gly Pro Pro Thr Val Pro Phe Leu Thr Pro Pro
          20          25          30
ttt gta tcc ccc aat ggg ttt caa gag agt ccc cct ggg gta ctc tct      144
Phe Val Ser Pro Asn Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser
          35          40          45
ttg cgc cta tcc gaa cct cta gtt acc tcc aat ggc atg ctt gcg ctc      192
Leu Arg Leu Ser Glu Pro Leu Val Thr Ser Asn Gly Met Leu Ala Leu
          50          55          60
aaa atg ggc aac ggc ctc tct ctg gac gag gcc ggc aac ctt acc tcc      240
Lys Met Gly Asn Gly Leu Ser Leu Asp Glu Ala Gly Asn Leu Thr Ser
65          70          75          80
caa aat gta acc act gtg agc cca cct ctc aaa aaa acc aag tca aac      288
Gln Asn Val Thr Thr Val Ser Pro Pro Leu Lys Lys Thr Lys Ser Asn
          85          90          95
ata aac ctg gaa ata tct gca ccc ctc aca gtt acc tca gaa gcc cta      336
Ile Asn Leu Glu Ile Ser Ala Pro Leu Thr Val Thr Ser Glu Ala Leu
          100          105          110
act gtg gct gcc gcc gca cct cta atg gtc gcg ggc aac aca ctc acc      384
Thr Val Ala Ala Ala Ala Pro Leu Met Val Ala Gly Asn Thr Leu Thr
          115          120          125
atg caa tca cag gcc ccg cta acc gtg cac gac tcc aaa ctt agc att      432
Met Gln Ser Gln Ala Pro Leu Thr Val His Asp Ser Lys Leu Ser Ile
          130          135          140
gcc acc caa gga ccc ctc aca gtg tca gaa gga aag cta gcc ctg caa      480
Ala Thr Gln Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Ala Leu Gln
145          150          155          160
aca tca ggc ccc ctc acc acc acc gat agc agt acc ctt act atc act      528
Thr Ser Gly Pro Leu Thr Thr Thr Asp Ser Ser Thr Leu Thr Ile Thr
          165          170          175
gcc tca ccc cct cta act act gcc act ggt agc ttg ggc att gac ttg      576
Ala Ser Pro Pro Leu Thr Thr Ala Thr Gly Ser Leu Gly Ile Asp Leu
          180          185          190
aaa gag ccc att tat aca caa aat gga aaa cta gga cta aag tac ggg      624
Lys Glu Pro Ile Tyr Thr Gln Asn Gly Lys Leu Gly Leu Lys Tyr Gly
          195          200          205
gct cct ttg cat gta aca gac gac cta aac act ttg acc gta gca act      672
Ala Pro Leu His Val Thr Asp Asp Leu Asn Thr Leu Thr Val Ala Thr
          210          215          220
ggc cca ggt gtg act att aat aat act tcc ttg caa act aaa gtt act      720
Gly Pro Gly Val Thr Ile Asn Asn Thr Ser Leu Gln Thr Lys Val Thr
225          230          235          240
gga gcc ttg ggt ttt gat tca caa ggc aat atg caa ctt aat gta gca      768
Gly Ala Leu Gly Phe Asp Ser Gln Gly Asn Met Gln Leu Asn Val Ala
          245          250          255
gga gga cta agg att gat tct caa aac aga cgc ctt ata ctt gat gtt      816

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cct gta aca cta acc att aca cta aac ggt aca cag gaa aca gga gac      1632
Pro Val Thr Leu Thr Ile Thr Leu Asn Gly Thr Gln Glu Thr Gly Asp
    530                      535                      540
aca act cca agt gca tac tct atg tca ttt tca tgg gac tgg tct ggc      1680
Thr Thr Pro Ser Ala Tyr Ser Met Ser Phe Ser Trp Asp Trp Ser Gly
545                      550                      555                      560
cac aac tac att aat gaa ata ttt gcc aca tcc tct tac act ttt tca      1728
His Asn Tyr Ile Asn Glu Ile Phe Ala Thr Ser Ser Tyr Thr Phe Ser
    565                      570                      575
tac att gcc caa gaa taa
Tyr Ile Ala Gln Glu ***
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<211>          120
<212>          PRT
<213>          Mus musculus
<400>          15
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Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
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Tyr Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Leu Val
    35                    40                    45
Ala Ala Ile Asn Ser Asp Gly Gly Ile Thr Tyr Tyr Leu Asp Thr Val
    50                    55                    60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                    70                    75
Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Leu Phe Tyr Cys
80                    85                    90                    95
Ala Arg His Arg Ser Gly Tyr Phe Ser Met Asp Tyr Trp Gly Gln Gly
    100                    105                    110
Thr Ser Val Thr Val Ser Ser Gly Ser
    115
<210>          16
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Asp Ile Val Met Thr Gln Ser Gln Arg Phe Met Ser Thr Thr Val Gly
1                    5                    10                    15
Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn Val Val Ser Ala
    20                    25                    30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
    35                    40                    45
Tyr Ser Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                    55                    60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Met Gln Ser
65                    70                    75                    80
Glu Asp Leu Ala Asp Phe Phe Cys Gln Gln Tyr Ser Asn Tyr Pro Trp
    85                    90                    95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala Ala

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	100	105	110
Pro Thr Val Ser			
115			