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(87)

2003 09 04

(30) 60/361,257 2002 02 28 (US)

(71) , 10111, , 2100, 630

06030 263

(72) , , 02453, , 18

, , 01832, , 23

, , 02144, , 58

, , 01845, , 707

, , 06001, , 70

(74)

:

(54)

ATPase

가

CD4+ T- (Raychaudhuri Morrow (1993) Immunology Today 14:344-348).

T- (CTL) CTL CD8+

DNA

CD8+ CTL

Srivastava 가 (1994) Curr.Op.Imbu. 6:728 ; Srivastava (1993) Adv. CancerRes. 62: 153).

(hsps)

hsp 1-5 hsp90, hsp70, hsp60, sm hsp (Srivastava, 2002,Annu.Rev.Immunol.20:395-425).

hsp

395-425 (Srivastava , 2002, Annu. Rev. Immunol.20: hsp

hsp (ER) (chaperon) hsp70 (Lindquist , 1988, Ann. Rev. Genetics 22: 631-677)

hsp pH (ATP) (methylcholanthrene)
 . Srivastava (inbred) (Srivastava, 1988, Immunol. Today 9: 78-83).

86kDa 96kDa (gp96) 84
 (Srivastava, 1986, Proc. Nat'l. Acad. Sci. USA 83 : 3407-3411; Ullrich, 1986, Proc. Nat'l. Acad. Sci. USA 83 : 3121-3125).

gp96 hsp84/86 가
 . gp96 hsp84/86 ER
 (counterpart) (Srivastava, 1988, Immunogenetics 28: 205-207; Srivastava, 1991, Curr. Top. Microbiol. Immunol. 167: 109-123).

가 hsp70 가
 . hsp70 (Udono Srivastava, 1993, J Exp. Med. 178: 1391-1396).
 가 (Srivastava, 1993, Adv. Cancer Res. 62: 153-177; Udono, 1994, J. Immunol., 152: 5398-5403; Suto, 1995, Science 269 :1585-1588).
 a (1998) Immunity 8: 657; Ciupitu, (1998) J. Exp. Med. 5: 685; Arnold (1995) J Exp. Med 182: 885).

gp96, hsc70, hsp84/hsp86 가
 (Nieland (1996) Proc. Nat'l Acad. Sci. USA 93: 6135; Breloer (1998) Eur. J Immunol. 28: 1016; Ishii 28 : 1016 ; (1999) J. Immunol. 162: 1303).

(Srivastava (1986) Proc. Nat'l. Acad. Sci. USA 83: 3407; Ullrich (1986) Proc. Nat'l. Acad. Sci. USA 83: 3121; Peng (1997) J. I. Meth. 204: 13; Basu Srivastava (1999) J. Exp. Med. 189: 797) (Tamura (1997) Science 278: 117; Yedavelli (1999) Int. J Mol. Med 3: 243) (Ciupitu (1998) J. Exp. Med. 5: 685).

가 gp96 (Janetzki (1998) J Immunother. 4: 26
 9; Amato, (1999) ASCO 1278; Lewis, (1999) ASCO 1687) hsp70
 (Menoret Chandawarkar (1998) Semin. in Oncology 25: 654)

104 hsp, hsp90, hsp70 hsp60 hsp ATPase 가 (Scheibel, (1997) J. Biol. Chem. 272: 18608-18613; Richter (2001) J. Biol. Chem 276: 33689 ; Lopez-Buesa, (1998) Proc. Nat'l. Acad. Sci. 95: 15253; Schirmer, (1998) J. Biol. Chem. 273: 15546).

hsp90 ATP 가 (Obermann (1998) J. Cell Biol. 143: 901 ; Panaretou (1998) EMBO J. 17: 4829). , hsp90 ATPase in vivo

hsp90 가 Gp96 ATPase (Liet (1993) EMBO J. 12 : 3143). , gp96 , ATP 가
 gp96 Wearsch Nicchitta ((1997) J. Biol. Chem. 272: 5152).
 gp96 ATPase
 . Wearsch, Voglino Nicchitta gp96 ATP ADP
 / (renaturation) 2 4
 가 ((1998) Biochem. 37: 5709). Gp96
 (Wearsch Nicchitta (1996) Prot. Exp. Pur. 7: 114).

gp96 (Sastry Linderoth, J. Biol.Chem 274: 12023).
 가 3 (Wassenbe
 rg, (2000) J. Biol. Chem. 275: 22806). , Wassenberg ATP ATPase
 가 , gp96- , gp96

(major histocompatibility) I gp96-

hsp- 가 hsp-
 hsp hsp gp96, hsp90, hsp70, (calreticulin),
 hsp10 grpl70 hsp (Srivast
 ava 1998, Immunity 8: 657- 665; Srivastava, 2002, Annu. Rev. Immunol. 20: 395-425). ,
 - gp96 가 gp96
 (Suto Srivastava, 1995, Science 269: 1585-1588), -
 gp96 (Arnold 1
 995, J. Exp. Med. 182 : 885-889 ; Breloer 1998, Eur. J. Immunol. 28 : 1016-1021).

(Tamura 1997, Science 278: 117-120) (Blachere 1997, J. E
 xp. Med. 186: 1183-1406) Hsp- hsp-
 CD8+ T- (Srivastava, 2002,
 Annu. Rev. Immunol. 20: 395-425). hsp
 , PCT WO 96/10411, 1996.4.11 WO 97/10001, 1997. 3. 20[
 5,750,119(1998 4 12), 5,837,251(1998 11 17)]

T WO 95/24923(1995 9 21) PC
 PCT WO 97/10000(1997 3 20; 6,030,618, 2000 2
 29)
 PCT WO 97/10002, 1997 3 20 ; 5,985
 ,270, 1999 11 16) hsp

hsp hsp70, hsp90, hsp60
 가, hsp hsp90, gp96(grp94), hsp 104, hsp 70 hsp 60
 hsp

가
 [(re-presentation)] T-

hsp-

t) -1(MCP-1) ; (NO) ; CD91(-2- (chemo)- (attractan
CD36 ; ; 2MR) /

(ATPase)
P, AMP / (immunoaffinity) , ATP , .ATPase
, , ATP, AD
, HPLC

/

가

(ATPase)
(ATPase)
(ATPase)
(ATPase)

(geldanamycin) NECA hsp
ATPase , ATPase (geldanamycin)
ATPase가

;

가
ATPase

ATPase

(subnormal)

ATPase

, ATPase

가

가

(subj

ect)

(ATPase)

(ATPase)

가

hsp ; hsp hsp- hsp-

(mass)

(ATPase)

(ATPase)

(instruction)

가

(disulfonic) ('bis-ANS'), (azidosalicylamido)]

가

4,4'-(hexanoate; SASD) (dianilino)-1,1'-(binaphthyl)-5, 5' (sulfosuccinimidyl) [4-

가 bis-ANS, 가

SASD가

(PEG')

gp96

가 hsp90

/(bispecific)

가

(streptavidin)

가 bis-ANS,

SASD가

가

가

gp96 hsp90 .

가 bis-ANS, hsp

SASD가 hsp-
가 bis-ANS, hsp

가
SASD가

bis-ANS,

SASD가

가

가

bis-ANS

SASD가

gp96

hsp90 .

가

SASD가

가

bis-ANS,

가

가

bis-ANS

SASD가

(a)

, (b)

, (c)

가

-

가

gp96

hsp90 .

(a)

가 bis-ANS,

SASD가

; (b)

가

(a)

가 bis-ANS,

SASD가

가

; (b)

가
gp96

hsp90 .

('hsp-

'hsp

')

hsp-

; 가

hsp . gp96- .

gp96 ATPase 가 , T
(NO) .

, MCP-1 6 , gp96 , MCP-1 , gp96

ATPase gp96 ; ATPase gp96
gp96 ATPase ; ATPase gp96

gp96 ATPase gp96 T-
gp96 ATPase gp96

가 hsp- hsp hsp- 가 가
hsp- 가 .

ATPase / hsp-

hsp hsp- ATPase hsp hsp-
가 , ATPase 가 hsp hsp- hsp 가 hsp- hsp-

-) T- (

(chemo)- (attractant) -1(MCP-1) (NO) ; CD91(-2-
, 2MR) / CD36 ; ;
;

'hsp' 'hsp-'

(1) 가
; (3) ATP

pH 가 가 ; (2)
1,2, 3, 4,5 6

35%

sp 60 hsp hsp- hsp hsp- . hsp hsp90, 70 hsp h
hsp90, 70 hsp hsp 60 hsp hsp . ATPase 가 hsp hsp- hsp
90, gp96(grp94), hsp 104, hsp 70 hsp 60 hsp
gp96 hsp gp96- hsp- hsp- grp94 .

hsp hsp- ATPase /
, ATP ATP , AMP, ADP 가 / 가 가
ATP가 ATPase . HPLC [- ³² P] 가
5.2 . (TLC) .

hsp hsp- / hsp

80 %

90 %

95 %

99 %

60 % hsp

70 %

80 %

90 %

99 %

95 %

SDS - PAGE

hsp

가

hsp'

hsp

hsp가

가

('MHC')

가 , ,

가

hsp70, hsp90, gp96,

(calreticulin), h

sp110, grp170,

hsp-

hsp

가

T-
가

T-

가

T-

가

hsp70, hsp90, gp96,

(calreticulin), hsp110, grp170,

가 5.15

가

가

가

, 8

가,

hsp70, hsp90, gp96,

, hsp110, grp170,

가

, (a)

가

; (b)

APC

, B

APC

APC

APC

(APC

)

가 (APC)

us) / 가 (autologo (biopsies) (allogeneic))

MHC (precancerous) (

가 가 가 가

5.1

(1) 가 ; (2) ; (3) ATP pH 가 가 1,2,3 ; 4,5 6 35% (modality) hsp-

hsp- hsp hsp 70, hsp 90, gp96, , hsp110 grpl70, hsp 70, hsp 90, gp96, , hsp110 grpl70

hsp MHC ((tyrosinase), gp100, (melan) (HIV -I), (HIV -II), A I(HSV -I), (rhinovirus), (rotavirus), (papova) (echinovirus)), (arbovirus), (huntavirus), (coxsackie)

T- hps hsp

, () (, ,)
 hsp , hsp- 가
 3, 4,5 6 hsp pH hsp- hsp ATP 1,2, . h
 sp (immortalized)
 hsp- hsp
 5.1.1 hsp- (source)
 hsp- hsp- . hsp-
 . hsp-
 , , 가 hsp- 가 . hsp-
 () (6,017,540).
 sp- (immortalized) hsp- . h
 T-
 , ,
 hsp- A , B , C , , (rhinovirus,
 I(HSV-I), (rotavirus), (echinovirus), (arbovirus), (papova) (huntavirus), (coxsackie)
 , , , HIV- I, HIV- II
 , 가 , hsp-
 hsp- , , (arghritis), , (epiglottitis), , (salpingiti
 s), , (shigella) , 가 (gastroenteritis)
 - (Mycobacteria), , (Neisseria) hsp hsp
 . hsp-
 (Leishmania), (Kokzidioa),
 . 가 hsp hsp-
 hsp- hsp hsp-
 , , ()
 hsp- (),
 e. , ; (myxosarcomas) ; (liposarcomas); ; ; (angiosarcomas) ;
 (endotheliosarcomas); (lymphangiosarcomas); (synoviosarcomas); (me
 sotheliosarcomas); (Ewing's tumors); ; ; (malignant lymphomas);
 ; ;

가 , () ; (basal cell carcinomas); (sweat gland carcinomas); ; (adenocarcinomas); ; ; (medullary carcinomas); (); (bronchogenic carcinomas); ; (melanocarcinomas); ; (hepatocellular carcinomas); (bile duct carcinomas); (papillary carcinomas); ; ; (choriocarcinomas); ; (seminomas); (embryonal carcinomas malignant teratomas) (teratocarcinomas) hsp hsp-

hsp hsp- [(myeloblastic)

(promyelocytic), (myelomonocytic), (monocytic) (erythroleukemia)]; [(granulocytic)] ; (polycythemia vera), [- (non-Hodgkin's disease)], (Waldenstrom's macroglobulinemia),

hsp- . hsp-

, hsp-

5.1.2 Hsp70-

hsp70- , Udono et al., 1993, J.Exp.Med. 178: 1391 - 1396

30mM pH 7.5 1mM (phenyl methyl sulfonyl fluoride, PMSF) 가 1X (Lysis buffer) > 99%

pH 7.5 1mM PMSF 20 , > 95% 30mM (Dounce homogenizer)

1,000g 10 100,000g 90 (PBS) (Con A Sepharose) 2mM Ca²⁺ 2mM Mg²⁺

ose) 2X 36 2 ~ 3 IOmM (Con A Sepharose) (Tris-Acetate) pH 7.5 17,000rpm

pm(Sorvall SS34 rotor) 20 pH 7.5, 20mM NaCl, 0.1mM EDTA 15mM 2- (2-mercaptoethanol) 20mM Mono Q FPLC 20mM 500mM NaCl (gradient) (SDS-PAGE) -hsp70 (N27F

3-4 , StressGen) -hsp70 , hsp70-

50 ~ 70% (cut) , 17,000 rpm (SS34 Sorvall rotor) , 70% 가 , Sephadex^R G25 (Pharmacia) hsp70 Mono Q F

PLC hsp70- 1mg / 1g hsp70-

SDS-PAGE
 (Pharmacia)
 550mM NaCl

60 ~ 95%
 5mM
 , pH 7

0 ~ 1M NaCl
 Mono Q FPLC
 gp96 400mM

가
 Mono Q FPLC
 DEAE-

가 50%
 가 70%

100,000g
 가 4 1/2 12
 6,000 rpm (Sorvall SS34 rotor)
 6,000 rpm (Sorvall SS34 rotor)
 6,000 rpm (Sorvall SS34 rotor)
 15,000 rpm (Sorvall SS34 rotor)

2mM Ca²⁺ Mg²⁺
 PBS
 PBS

gp96
 G25
 5mM
 5mM
 , pH 7, 300mM NaCl
 DEAE-
 280nm
 가
 5mM
 5mM
 , pH 7, 300mM NaCl
 175mM
 , pH 7
 5mM
 , pH 7, 700mM NaCl
 5mM
 Mono Q F

PLC (Pharmacia)
 , pH7
 , Mono Q FPLC (Pharmacia)

가
 가 가 가
 가 가

gp96 100,000g
 e) 1%
 1
 2+ Ca2+)
 gp96-

(, Mg2+ Ca2+)
 20,000g 30
 가 100,000g 90
 2mM

(sodium deoxycholate)
 PBS (Mg

gp96- 1g /
 10 ~ 20µg gp96

gp96- hsp ATP pH 가
 gp96- ATP gp96- gp96- pH
 hsp hsp-

5.1.5 Hsp110-

Wang et al., 2001, J. Immunol. 166(1):490-7

(40~60ml)

5

(30 m

N 2 , pH7.2) 4,500x g 100,000x g
 (Pharmacia) (20mM -H
 Cl, pH 7.5; 100mM NaCl; 1mM MgCl₂; 1 mM CaCl₂; 1 mM MnCl₂; 15 mM 2-ME) -
 (Con A-Sepharose column, Pharmacia Biotech, Piscataway, NJ) 15%
 -D-o- (methylmannoside)(Sigma, St. Louis, MO)
 20 mM Tris-HCl, pH 7.5; 100 mM NaCl; 15 mM 2-ME
 , DEAE- , 100 500mM NaCl . hs
 p110 , 20mM Tris-HCl, pH 7.5; 200 mM NaCl ; 15 mM 2-ME
 Mono Q (Pharmacia) 10/10 200-500 mM NaCl
 Wang et al., 1999, J.Immunol. 162:3378 hsp110 Ab
 SDS-PAGE . hsp110 (Amicon, Beverly, MA)
 (Superose) 12 (Pharmacia) 0.2ml/min 40mM Tris
 -HCl, pH8.0; 150mM NaCl; 15mM 2-ME

5.1.6 Grp-170-

Wang et al.,2001,J.Immunol.166(1):490-7

(40~60ml) 5 (30 m
 N 2 , pH7.2) 4,500x g 100,000x g
 (Pharmacia) (20mM -H
 Cl, pH 7.5; 100mM NaCl; 1mM MgCl₂; 1 mM CaCl₂; 1 mM MnCl₂; 15 mM 2-ME) -
 (Con A-Sepharose column, Pharmacia Biotech, Piscataway, NJ) 15%
 -D-o- (methylmannoside)(Sigma, St. Louis, MO)
 20 mM Tris-HCl, pH 7.5; 150 mM NaCl
 Mono Q (Pharmacia) 150 400 mM NaCl
 (Superose) 12 (Pharmacia) grp170

5.1.7 HSP

hsp
 (expression construct) hsp 가 (Operably-
 associated)' 가 hsp 가 가
 hsp (ATG) , RNA
 hsp , RNA TATA 가 , CAAT 5' 가
 3'
 DNA hsp 가 , hsp
 (Wu et al., 1987, Methods in Enzymol, 152: 343-349) cDNAs
 DNA
 PCR DNA DNA

가 hsp hsp- 5,580,859 DNA

hsp hsp (cosmid), (phagemid) hsp

가 hsp hsp- hsp hsp- 1 ~ 2

가 hsp가

hsp hsp hsp

hsp hsp-

5.1.8

hsp (synthesizer) hsp hsp

hsp Merrifield, 1963, J.Am. Chem.Soc., 85: 2149 N

- - C- (support) 가 N- (deprotected) N- (dicyclohexylcarbodiimide) 가 Boc Fmoc

가 N- (Atherton, , 1989, Solid Phase Peptide Synthesis: A Practical Approach, IRL Press Bodanszky, 1993, Peptide Chemistry, A Practical Textbook, 2nd Ed. , Springer-Verlag)

hsp / prep. HPLC

5.2 (ATPase)

hsp hsp- hsp h

sp hsp- hsp hsp- hsp h

sp- hsp- hsp- hsp- hsp hsp

hsp- (geldanamycin) hsp (ethylcarboxamido)- (NECA) (5'-N-

가

, ATP, ADP / AMP
, ATP, ADP, AMP /

ATP

(Millipore BIOMAX) (10 Kda MWCO) 500 µg/ml
20% DMSO 400 µ M 20% DMSO
Gp96(1µg)) 37 4
ATP (10-30) 50 µ L ATP Molecular Devices Lmax
PBS 100 µ L ATP DMSO DMSO/
ROCHE CLII bioluminescence ATP gp96 ATP 가
NECA

~5mg/mL gp96 PBS 5 mM MgCl2 25 mM KCL 37 ATP 10X
ATP 1:1, 2:1, 5:1, 10: 1 HPLC
(casein kinase) II ATP 가 ATP

0.5 U/mL II (ATP 1:1, 1:2, 1:
5, 1:10) 20µg/mL ATP, 2mg/mL , 37 10mM MgCl2, 130mM KCL 5mM
DTT 40mM HEPES , ATP

ATP Partisil SAX (2.1 x 250 mm, 10µm, Alltech) HPLC
0.3-1 M 가 0.25 mL/min 25
215nm 가 Waters Alliance HPLC . ATP ADP AMP
gp96 mg 가 ATP (nmol/mg/hr) II
gp96 II ATP 가 ATP (nmol/U/hr) (background) 가

, [- ³² P]- ATP
(Li and Srivastava (1993) EM

BO J. 12: 3143; Wearsch and Nicchitta (1997)J. Biol.Chem. 272: 5152):

, 1µg gp96 hsp 70 20 µ M [- ³² P] ATP 20mM HEPES, pH 7.2, 20mM NaC
L 2mM MgCl2 20µl 37 1 , 1µl
(PEI) 1M LiCl 1M HCOOH 1:1
[- ³² P] ATP [- ³² P] ADP [- ³² P] AMP
[ADP + AMP]/ [ATP + AMP + ADP] x 100% 가 ATP gp96
hsp70 ATP 가

HPLC

Gp96(2µg ; 200 µg/ml in PBS) ATP (160 µ M), 10mM MgCl2 20% DMSO PBS

가 . , DMSO (160 μ M) DMSO . 37
 4 , 80μℓ 100mM KH2PO4 (pH 4.0)가 가 ,
 HPLC . ADP 1% 60 mM KH2PO4 (pH 6.0)
 Aquasil C18 column (250 mm x 4.6 mm) ATP . 0.5 ml/min . AD
 P (peak integration) ADP .

hsp hsp-

5.3

, hsp hsp- hsp hsp- hsp hsp-
 hsp hsp- hsp- hsp-
 hsp hsp- hsp- hsp-
 hsp hsp

hsp

ol.Chem. 274: 4133-4139 가 , Chadli etal., (1999)J. Bi

FPLC (Amersham Pharmacia Biotech) 4 50mM Tris-HCL,
 pH 8.65 (Superose)6 12 10/30 0.2 ml/min
 280nm UV
 (Amersham Pharmacia Biotech) (thyroglobulin)(669
 kDa), (ferritin) (440 kDa), (catalase) (232 kDa), (aldolase) (158 kDa),
 (bovine serum albumin) (67 kDa) (chymotrypsinogen) (25kDa)

, SDS Native PAGE가 , Chadli etal., (1999)J. Biol.Chem. 274:
 4133-4139 :

SDS Native PAGE (Phast) (Amersham Pharmacia Biotech)
 (Amersham Pharmacia Biotech) (phosphorylase b) (94 kDa), (bovine
 serum albumin) (67 kDa), (ovalubumin) (43 kDa), (carbonic anhydrase) (30 k
 Da), (soybean trypsin inhibitor) (20 kDa) - (-lactalbumin) (14.4 kDa)

Native PAGE 4 II(Multipore II) (Amersham Pharmacia Biotech) 10%
 , 375 mM , pH 8.9 (thyrglobulin) (669 kDa), (f
 erritin) (440 kDa), (catalase) (232 kDa), (lactate dehydrogenase) (140 k
 Da) (bovine serum albumin) (67 kDa) (Amersham Pharmacia Biotech)

(Millipore)

(native) PAGE hsp (electrotransferred). -
 PBS, 0.05% Tween 20 (PBST) 10% 2 , PBST , 2
 -hsp90 Ab119 (37) (1: 4000) d7 (28) (1: 4000) , PBST , 1
 (anti - rabbit) (anti - mouse) , PBST , ECL (Amersham Pharmacia
 Biotech)

hem.35: 16760-9 가 , Wearsch and Nicchitta (1996)Bioc
 :

TSK-GEL g3000 SW (Tosohaus, Montgomeryville, PA) PBS(phosphate buffered saline)
 A(110 mM KOAc, 25nM K-HEPES, pH 7.2, 20 mM NaCl, 1 mM Mg(OAc)2, 0.1 mM CaCl2)
 . 125µl 0.6 mL/min . 0.5 mL SDS-PA
 GE (Stokes radius, Rs) (, Rs = 8.5nm, 660 kD
 a; ,Rs= 3.5nm, 66 kDa; ,Rs = 3.1nm, 43 kDa)
 , grp94 45 125µl A 1 x PBS 4 mM Zwittergent 3-12

2 , Wearsch and Nicchitta (1996) Prot. E
 xp. Pur.7:114-121

() 0.5 M , 5% SDS, 0.01% , 55 10 가
 grp94 1µg 50 mM DTT . 5
 IgG7† 7.5% , Mini-Protean
 II 2-D Cell (Bio-Rad) 200V , 0.5 M , 5% SDS, 0.1 M DTT 15
 55 , 7.5% (preparative slab gel)
 (Coomasie)

hsp hsp-
 , Wearsch and Nicchitta (1996)Biochem.35 : 16760-9

Native grp94,
 - (elastase-digested) grp94, grp94- C () A 15~30
 % grp94-Cexp grp94-MBP PBS
 10~25% . 11.5 mL Auto Densi-Flow IIc (Buchler Instrum
 ents, Lenexa, KS) . 200µl , Beckman SW41 rotor 4
 0,000 rpm, 20 (Catalase) (11.3 S), (yeast alco
 hol dehydrogenase) (7.4 S), BSA (4.3 S), (ovalbumin) (3.5 S), A(chymotrypsinog
 en A) (2.6 S)† . 0.5 mL , SDS-PAGE (grp94) 280
 nm ()

gp96 / gp 96

gp96 / gp96 /

gp96 / gp96

gp96 / gp96

gp96 / gp96

5.4

hsp / hsp- hsp / hsp
 hsp- hsp /
 () T ;
 CD91 (alpha-2-macroglobulin receptor, 2MR) / CD36 -1(MCP-1), (NO);

, 1999.11.16) , 가 hsp hsp- 60/232,779 ; 09/693,643

5.5

5.6

(subject)

가

가

(thenon-antigenic spec

ific aspects) /

가

hsp / hsp-
hsp / hsp-

5.7 HSP Hsp- ES

가

hsp hsp- ((, , 가))

5.8

hsp hsp- hsp hsp- hsp-
(uncontacted) 가 가

(, 17
(Rosser et al., J. Bio. Chem. 2000,275 :

5.12

가, hsp- /
 가, hsp
 가, hsp/ - ()
 가, hsp/ - 가, hsp/ - ()
 (ATP, / -)
 (guanidium hydrochloride) /
 ()
 ()가
 5.18

5.18

가

5.18

가

(fluorescence activated cell sorting) ()
)
 ()

(, KS 1/4) (Perez and Walker, 1990, J. Immunol. 142: 3662-3667; Bupal, 1
 988, Hybridoma 7 (4): 407-415); (CA125) (Yu, et al., 1991, Cancer Res. 51 (2): 468-475);
 (prostatic acid phosphate) (Tailer, et al., 1990, Nucl. Acids Res. 18 (16): 4928);
 (Henttu and Vihko, 1989, Biochem. Biophys. Res. Comm. 160 (2): 903-910; Israeli, et al., 1993, Cancer
 Res. 53: 227-230); (melanoma)- p97 (Estin, et al., 1989, J.Natl.CancerInst. 81 (6): 445-446);
 gp75 (Vijayasardahl, et al., 1990, J. Exp.Med. 171 (4): 1375-1380); (Natali,

etal., 1987, Cancer 59: 55-63)

(12,13, 59 61) (Gedde-Dahl et al., 1994, Eur. J. Immunol. 24 (2): 410-414))
 , p53, T- p53
 (Gnjatic et al., 1995, Eur. J. Immunol.25 (6): 1638-1642)

가
 (hepatitis) A, B, C, I(HSV-I),
 (HSV-II), (rinderpest), (rhinovirus),
 (echinovirus),
 (huntavirus), (coxsackie) (mumps) (measles)
 (smallpox) (rubella) I(
 HIV-I), (HIV-II)

가
 (Barcillus anthracis) (Erysipelothrix)),
 (Bartonella, Brucella, Campylobacter, Enterobacter, Escherichia, Francisella, He
 mophilus, Klebsiella, Morganella, Proteus, Providencia, Pseudomonas, Salmonella, Serratia, Shigella, Vibrio,
 Yersinia), (spirochete) (Leptospira) B
 orrelia burgdorferi), (C.tetani, C.botulinum, C.perfingens
 Actinomyces Clostridium), (coccal) Streptococcus , Pneumoc
 occus , Staphylococcus (S. aureus S. pneumonia), Neisseria species(N. meningitid
 is)

가
 gillus)(Aspergillus fumigatus), (Cryptococcus)(Cryptococcus neoformans)),
 Sporotrix, Coccidioides, Paracoccidioides, Histoplasma, Blastomyces, Candida(Candida albicans), R
 hizopus, Rhizomucor, Absidia Basidiobolus

(helminth) 가 (protozoa), (nematode)
 (Entoamoeba), (Plasmodium), (Leishmania),
 (Eimeria), (Cryptosporidium), (Giardiasis), (Toxoplasma)
 (Trypanosoma species)

5.12.1

가
 (cytosol)

가 Current Protocols in Immunology, vol. 2, chapter 8, Coligan et al.(ed.), John
 Wiley amp; Sons, Inc.; Pathogenic and Clinical Microbiology: A Laboratory Manual by Rowland et al., Little B
 rown amp; Co. , June 1994;

20, 50, 100, 500, 1,000, 5,000, 10,000, 20,000

(cytosol)

20, 50, 100, 500, 1,000, 5,000, 10,000, 20,000

hsp

hsp

가

(가

)

mM 20 pH 7.5 1mM PMSF 3 1X (Lysis buffer) 30
 nce homogenizer) 가 > 99% (shearing) > 95% (Dou
 1,000Xg 10 1mM PMSF (PBS) 가
 100,000Xg 1 36 4 PBS 100,000Xg (3
 100).

30mM pH 7.5 1mM PMSF 3 1X (Lysis buffer)
 20 (Dounce homogenizer) (shearing) > 95%
 가 > 99% 1mM PMSF (PBS)

1,000Xg 10
 100,000g (1% -) PBS(Ca²⁺ Mg²⁺) 5
 20,000g 30 PBS(Mg²⁺ Ca²⁺) 가
 100,000g 90 가 2mM가

hsp

5.12.2

가
 ccocal peptidase) I ((elastase), (Staphylococcal) I, MHC- 가
 V8 (papain), (cathepsin) G, (Staphyloco (thermolysin)
 가 (cyanogen)
 가 hsp
 가 가 (Staphylococcal) I
 가 hsp
 PMSF, (amastatin), 가 (leupeptin), (cystatin)
 가

가 hsp / MHC I II hsp ATP pH hsp- hs

p hsp- : hsp- Centricon 10 assembly (Millipore) HPLC SDS-PAG 10mM ATP (TFA) hsp- 30 가 가 10% (vol/vol)가 (Van Bleek, et al., 1990, Nature 348: 213-216; and Li, et al., 1993, EMBO Journal 12: 3143-3151).

H Centricon 10 assembly ATP p , 0.1% TFA VYDAC C18 , 0.1 % TFA (HPLC) 0.1% TFA 0 80% OD210 , 0.1% TFA 0.8 ml/min

MHC- MHC- , Falk, et al., 1990, Nature 348: 248-251 ;Rotzsche, et al., 1990, Nature 348: 252-254; Elliott, et al., 1990, Nature 348: 191-197; Falk, et al., 1991, Nature 351: 290-296; Demotz, et al., 1989, Nature 343: 682-684; Rotzsche, et al., 1990, Science 249: 283-287,

,MHC- 0.1% TFA HPLC MHC- Merrifield, 1963, J.Am. Chem.Soc., 85: 2149 N- - C- 가 N- - (deprotected) N- - 가 Boc Fmoc . 가 N- -

, C- N- 가 , N- 가 N- 가 (Atherton, et al., 1989, Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Bodanszky, 1993, Peptide Chemistry, A Practical Textbook, 2nd Ed. , Springer-Verlag).

preparative HPLC, /

5.12.3

ISA (enzyme linked immunosorbent assay), (immunoassays), (immunoradiometric assays), (western blots), (assays), A , T-cell-

(Norrby, 1985, Summary, in Vaccines 85, Lerner, et al. (eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, pp. 388-389), (antisera) /

5.13 hsp/

hsp 가 가 , hsp

가 ,

hsp hsp ATP pH ATP 가 (apyranase) 가 , Levy, et al., 1991, Cell 67 : 265-274 pH 가 , pH 가 가 (1µg) hsp(9µg) 5 :1 가 , pH 7.2, 350mM NaCl, 3mM MgCl2 ImM Centri 4 45 15 3 (PMSF) 20mM hsp- con 10 (Millipore) SDS-PAGE MHC-

NaCl, 3mM MgCl₂ 1mM ADP, 5-10, 100, hsp 20mM, 37, 1, hsp70, pH 7.5, 0.5M
 5, 0.5M NaCl, 3nM MgCl₂, 5-10, gp96, hsp90, 20mM, 5-20, gp96, hsp90, pH 7.
 Centricon 10 (Millipore)

(mixed lymphocyte target cell assay) (MLTC)
 가

5.14 hsp

2 hsp hsp
 가 (cross-linker)' 가 (cross-linking agent)' . 가
 hsp-2

가 (bifunctional), (hetero-functional)(homo-functional)(trifunctional), homobifunctional
 가 가 가 가 가 가 가 가 가 가

(Biotinylation) (haptenylation) 2가(2)
 가 가

(IgG) (Avidin), (avidin), (streptavidin), (NeutrAvidin) G
 (biotin-binding protein) (CaptAvidin)
 4 가 가 가 가

hyde), (glutaraldehyde), (diacid chlorides)
 (Azidophenyl glyoxal monohydrate) (APG); 1,8-bis-(3-maleimidopropionyl)-2-hydroxy-1,3-propanediamine; PEG (p-nitro-phenyl carbonate) (Dimethyl suberimidate dihydrochloride) (DMS) 가
 (1,8-bis-Maleimidopropionyl)-2-hydroxy-1,3-propanediamine; PEG (p-nitro-phenyl carbonate) (Dimethyl suberimidate dihydrochloride) (DMS) 가
 St. Louis, MO), Pierce Biotechnology, Inc. (Rockford, IL) Molecular Probes (Eugene, OR) Sigma (

, 가 (PEG), (triflate), (tresylate), (aziridone), (oxirane), ()
 , ,)- (PEG-MAL) PEG(maleimido monomethoxy PEG) NHS- (PE
)- (PEG-MAL) PEG (mPEG-MAL) 1 2 가
 , 가 가 , 1 가 N- 2
 -S- - (SATA), N- -3- (2-) (SPDP), 4
 -(N-) -1- (SMCC), 4- (N-) -1-
 (sSMCC), 2- (Iminothiolane) (Traut's);N- [-]
 (AMAS);N- - (BMPPA);N- [-]
 TFA (BMPH); 1- -3- [3-] (EDC);[N-e-
] (EMCS); N- [g-] (GMBS);m-
 -N- (MBS) N- (Succinimidyl iodoac
 etate) (SIA) 가 가
 lar Probes (Eugene, OR) Sigma (St. Louis, MO), Pierce Biotechnology, Inc. (Rockford, IL) Molecu
 가
 , 가 가 가
 - [()] (THPP) 가 가
 (TSAT) Sigma (St. Louis, MO), Pierce Biotechnology, Inc. (Rockford, IL) Molecula
 r Probes (Eugene, OR) 가
 가 가 , 가
 , 가 (streptavidin-biotin linker) .
 , 2 , 1 /
 , 1 2 , .
 , 1 2 , 가 , 2가(2 (bispecific)) . 2
 , 1 2 , , 1 2 ,
 , hsp-
 , pH
 , 가 Sigma (St. Louis, MO; Sigma catalog,
 2002-2003, pages 573-580), Pierce Biotechnology, Inc. (Rockford, IL; Pierce Biotechnology, Inc. catal
 og, 2001-2002, pages 294-334) Molecular Probes (Eugene, OR; see Molecular Probes Handbook, 9
 th ed., 2002, chapter 5)

가 (SASD)가 (4-BAG (Takayama and Reed, 2001, Nature Cell Biology 3:E237-E241)

8- (8-ANS') 4, 4'-N- -1,1'- -5, 5'- ('bis-ANS'), 1 (ethylcarboxamidoadenosine)('N ECA') (Gewirth et al., U. S. Patent Application Publication No. 2002/0160496).

5.15 HSP-

5.15.1 MLTC

hsp-hsp- 7-10 10 가 가 8x10⁶ 4x10⁴ (mitomycin) C (5-10,000 rads) 10% 3ml RPMI 33% 2 (Glasebrook, et al., 1980, J Exp. Med. 151: 876). T T 가 T-

6 4 ⁵¹Cr- (Palladino, et al., 1987, Cancer Res. 47: 5074-5079 and Blachere, et al., 1993, J. Immunotherapy 14: 352-356). 가 : (E:T) (1:1 40:1) 20 m Ci ⁵¹Cr/ml 37 , 1 1x10⁶ 3 (E: T) 가) 100% (. 4 ⁵¹Cr) 200g 5 cpm cpm cpm cpm

MHC I , K-44 (-MHC I) 가 12.5%가 가

5.15 . 2CD4+ T-Cell

1 T- en) , CSF , FICOLL-PAQUE PLUS (Pharmacia, Upsalla, Swed Kruse and Sebald, 1992, EMBO J.11: 3237-3244. 7-10 가 24 48 가 , RPMI 1640 (GibcoBRL, Gaithersburg, Md.) . 5x 10⁴ T- / (PHA-blasts) 96 10% , 10 mM HEPES, pH 7.5, 2 mM L- , 100 units/ml G 100µg/ml (streptomycin sulphate) RPMI 1640 72 37 , 6 1 µCi ³H- (DuPont NEN, Boston, Mass.)/ , TOPCOUNT (Packard Instrument Co. , Meriden, Conn.)

5.15.3

hsp-
 , microtitre plates (96-well Immuno Platell, Nunc) (A 42)
 hsp- 0.75µg/ml 50µl/ PBS 4 , 16 20
 , 1 200µl PBS-T-BSA (0.05% (v/v) TWEEN 20 and 1% (w/v) bovine serum albumin
 PBS) 20 1 PBS-T 3 ()
 CSF 50µl/ 20 1 , 50- 20
 PBS-T 3 ,
 1 PBS-T-BSA 1:1,500
 (Amersham) , (3 PBS-T) 50µl o- (OPD)-H₂O₂
 5 2M H₂SO₄ 150µl , 492 nm(ref. 620nm) KontronSL
 T-210 photometer (SLT Lab-instr., Zurich, Switzerland)

5.15.4

hsp- CD4+ T-
 IFN- , , hsp-
 FITC- -CD8 PerCP- -CD4 T- - , I
 FN- (PE-anti-IFN-)
 , , - (ELISPOT) 가 T-
 - 1 , , -IFN- , microtiter
 . hsp-
 microtitre plate - 2 -
 가 가 (enzyme-conjugated streptavidin-cytokine-secreting cells)

5.15.5

, ' (Altman et al. , 1996, Science 274: 94-96) - T- MHC
 가 , MHC- hsp- T-
 , T-

5.16

/
 (U. S. Patent No. 5,985, 270, issued November 16,1999)
 , APC () hsp-
 , APC hsp- hsp- APC
 , hsp- hsp- ,

5.16.1

Inaba, K., et al., 1992, J. Exp. Med., 176: 1693-1702

rogenerator) (p

APC
 가
 :
 Ficoll-Hypaque ()
 AB + 37 1
 가 (4)
 1 mM EDTA가 가 15 , RPMI
 , RPMI . K., et al., 1992, J Exp. Med., 176: 1693-1702
 가 (M-CSF) 37 ; 가
 가 (GM-CSF)

5.16.2 APC hsp-

APC hsp . AP
 C 37 15 24 hsp- hsp
 ml 100 , 4x10⁷ ml 10
 PMI hsp90- 37 15 24 gp96-
 1 x 10⁷ /ml) (가) . APC가 1ml R
 (APC가
 APC가, CTLs T- CTLs (CTL)

5.16.3 APC

hsp- - APC 가
 10⁶ 10¹²
 IFN- , IFN- , IL-2, IL-4, IL-6, TNF
 가

5.17

hsp-

5.18

hsp / -
 (treatment)' (treating)'
 가
 가
 (prevention)' (preventing)'

(TLR-2, TLR-7, TLR-8 TLR-9; LPS; 41BB ,OX40 , ICOS, CD40 (Toll); (Fas ligand),PD1, CTLA-4 (peptidomimetic)

(mitogenic) CpG (motif) Woolridge, et al., 1997, Blood 89: 2994-2998 WO01/22972 , WO01/51083 , WO98/40100 WO99/61056 6,207,646 , 6,194,388 , 6,218,371 , 6,239,116 , 6,429,199 6,406,705 가 (phosphorothioate) Kandimalla et al. 'Effect of Chemical Modifications of Cytosine and Guanine in a CpG-Motif of Oligonucleotides: Structure-Immunostimulatory Activity Relations hips.' Bioorganic amp; Medicinal Chemistry 9: 807-813 (2001) 가 CpG 가 CpG (Th2) (IgG1>>IgG2a). 20010044416 A1 가 (internucleotide) 가 (adjuvant) 가 (depot) (alum)(); Montanide (Montanide IS (water A 720, AirLiquide, Paris, France) Seppic ISA ; MF-59 (85 -in-oil) (oil-in-water) ; Chiron Corporation, Emeryville, Calif.); PROVAX (80 -in-); IDEC (Pharmaceuticals Corporation, San Diego, Calif.)

가 CpG ; [((carboxylatophen)-) Q. saponaria ; QS21 (PCPP polymer; Virus Research Institute, USA); A(MPL; RibImmunoChem Research, Inc., Hamilton, Mont.), (muramyl dipeptide)(MDP; RibImmunoChem Research, Inc., Hamilton, Mont.), (threomyl)- (t-MDP; RibImmunoChem Research, Inc., Hamilton, Mont.) (LPS) ; OM-174(A ; OM Pharma SA, Mey rin, Switzerland); (Leishmania elongation factor) (; Cori xa Corporation, Seattle, Wash.), (AGP; Corixa Corporation, Seattle, Wash.)

가 가 ISCOMs (; CSL, Melbourn e, Australia); SB-AS2 (SmithKline Beecham adjuvant system #2, MPL QS21 ; SmithKline Beecham Biologicals[SBB], Rixensart, Belgium); SB-AS4 (SmithKline Beecham adjuvant sy stem #4, alum MPL ; SBB, Belgium); CRL 1005((flanked) ; Vaxcel,Inc., Norcross, Ga.) - ; Syntex (SAF, 80 ; Syntex Chemicals,Inc., Boulder, Colo.)

CpG (PCT WO99/61056),
 : (CT), CT B (CTB)(Wu et al., 1998, Tochikubo et al., 1998); CTD53 (Val to Asp) (Fontana et al., 1995); CTK97 (Val to Lys) (Fontana et al., 1995); CTK104 (Tyr to Lys) (Fontana et al., 1995); CTD53/K63 (Val to Asp, Ser to Lys) (Fontana et al., 1995); CTH54 (Arg to His) (Fontana et al., 1995); CTN107 (His to Asn) (Fontana et al., 1995); CTE114 (Ser to Glu) (Fontana et al., 1995); CTE112K (Glu to Lys) (Yamamoto et al., 1997a); CTS61F (Ser to Phe) (Yamamoto et al., 1997a, 1997b); CTS106 (Pro to Lys) (Douce et al., 1997, Fontana et al., 1995); CTK63 (Ser to Lys) (Douce et al., 1997, Fontana et al., 1995)
 , CT ; *Zonula occludens* , zot, - (labile)
 (Labile Toxin)(LT), LT B subunit (LTB) (Verweij et al., 1998); LT7K (Arg to Lys) (Komase et al., 1998, Douce et al., 1995); LT61F (Ser to Phe) (Komase et al., 1998) ;LT112K (Glu to Lys) (Komase et al., 1998) ; LT118E (Gly to Glu) (Komase et al., 1998); LT146E (Arg to Glu) (Komase et al., 1998); LT192G (Arg to Gly) (Komase et al., 1998); LTK63 (Ser to Lys) (Marchetti et al., 1998, Douce et al., 1997, 1998, DiTommaso et al., 1996); LTR72 (Ala to Arg) (Giuliani et al., 1998) , LT , PT-9K/129G (Roberts et al., 1995, Cropley et al., 1995) , PT(Lycke et al., 1992, Spangler BD, 1992, Freytag and Clements, 1999, Roberts et al., 1995, Wilson et al., 1995); () (Holmgren et al., 1993, Verweij et al., 1998, Rappuoli et al., 1995, Freytag and Clements, 1999); A () (A, MPL) (Sasaki et al., 1998, Vancott et al., 1998); (MDP) (Fukushima et al., 1996, Ogawa et al., 1989, Michalek et al., 1983, Morisaki et al., 1983); (*Borrelia burgdorferi* A (OspA) , *Neisseria meningitidis* (Marinero et al., 1999, Van de Verget al., 1996); (MF59) (Barchfield et al., 1999, Verschoor et al., 1999, O'Hagan, 1998); (Isaka et al., 1998, 1999); (QS21) Aquila Biopharmaceuticals, Inc., Worcester, Me.) (Sasaki et al., 1998, MacNeal et al., 1998), ISCOMs, MF-59 (a squalene-in-water emulsion stabilized with Span 85 and Tween 80; Chiron Corporation, Emeryville, Calif.); Montanide Seppic ISA (Montanide ISA 720; AirLiquide, Paris, France); PROVAX (; IDEC Pharmaceuticals Corporation, San Diego, Calif.); Syntex (SAF; Syntex Chemicals, Inc., Boulder, Colo.); [((carboxylato phenoxy)) (PCPP polymer; Virus Research Institute, USA) (Corixa Corporation, Seattle, Wash.)

5.18.1

(fibrosarcoma), (liposarcoma), (chondrosarcoma), (synovioma), (mesothelioma), Ewing's tumor, (leiomyosarcoma), (squamous cell), (papillary carcinoma), (cystadenocarcinoma), (bronchogenic), (choriocarcinoma), (s eminoma), Wilms (astrocytoma), (medulloblastoma), (craniopharyngioma), (ependy moma), (pinealoma), (hemangioblastoma), (acoustic neuroma), (oligodendroglioma), (meningioma), (melanoma), (neuroblastoma), (retinoblastoma) (sarcoma) (carcinoma), (myeloblastic, promyelocytic, myelomonocytic, monocytic erythroleukemia) ; () ; (Hodgkin -Hodgkin), (multiple myeloma), Waldenstrom (macroglobulinemia), (heavy chain disease)

가 hsp- hsp- (sensitized) APC 가 가

가

가

가

(immunocompetence)

가

(acicivcin);

(batimastat);

(bisnafide dimesylate);

(dexormaplatin);

(droloxifene);

(eflornithine)

-2a;

-2b;

-n1;

-n3;

II (

-1a;

II

-1b;

rIL2);

가

가

가

가

(porifmer)

(sulofenur);

가

20-epi-1,25

D3; 5-

; ALL-TK

D;

G;

(dorsalizing)

-1;

-CDP-DL-PTBA;

1;

2;

3;

III

; BCR/ABL

A;

B;

; bFGF

(reflate);

(canarypox) IL-2;

(ICOS);

; CaRest M3; CARN 700;

B;

A; B; A4; 816;
8; A; A;
(cytarabineocfosfate);
B; -5- 9-; SA; B;
가
가
- 1
4-; F; -N; 가; B;
+
7; A; 가; RNA;
MIF; A+; sk; B;
N-; 1-; N-; +
06-
가; 가; A; B;
C; -; J2; A-; raf;
; ras; ras; ras-GAP;
Re 186; RII; SarcNU; A; Sdi 1 (mimetics);
B1; 1;
D; 1;
(superactive vasoactive intestinal peptide antagonist);
가 (tegafur);
(mimetics);
UBC; B;
(vinxaltine);
(stimalamer);
DNA; 1;

[1-1]

: (Nitrogen mustards)	(cyclophosphamide)
:	(BCNU)
	(CCNU)
:	
:	

:	
(Taxoid):	
<u>DNA</u>	
:	
	9-
:	C

- (anti-folate)	
DHFR :	
IMP :	
	EICAR

:	

:	
:	5-
	(floxuridine)
:	(ara C)
:	
DNA	3 - HP
	2' - -5-
	5 - HP
	- TGDR
	ara - C
	5 - -2' -
	- TGDR

	II
- : (antimitotic agents)	
	B
	10
	(rhizoxin)

--

(isoprenylation inhibitor)	
:	1- -4-
:	
:	D
:	A2
:	B2
:	
:	()
:	
:	
:	
MDR :	
Ca ⁺² APTase :	가 (Thapsigargin)

(FLAG, CHOP) . FLAG
(Ara-C) G-CSF . CHOP ,
TIN , IL-2, / 5- VP-16() , HERCEP
() /
G), / 6- (MYLOTAR
(CML), Hsp- hsp70-
GLEEVEC™
(dacarbazine)
(irinotecan)
/ -Hodgkin , CHOP,

(gemcitabine)

100 1000mg/m²
/cycle 200 4000mg/m²/cycle
700 1000mg/m²/cycle
25 50mg/m²/cycle
200 2000mg/m²/cycle (Ara-C)
1.5 7.5mg/m²/cycle 5 1
5mg/m²/cycle 5 20mg/m²/cycle 5
2 8mg/m²/cycle
40 160mg/m²/cycle (epipodoph
yllotoxin) 50 200mg/m²/cycle
50 75, 75 100, 100 125, 125 150mg/m²/
cycle 3.7 5.4, 5.5 7.4, 7.5 1
1, 11 18.5mg/m²/cycle 0.7
1.4, 1.5 2mg/m²/cycle 3.3
5, 5 10, 10 100, 100 1000mg/m²/cycle

가

가

(6 60mg/m²/day)
(10 135mg/m²/day)
2.5 25mg/m²/day)
(0.5 1.5mg/m²/day) (Ara-C)
) 10 100mg/m²/cycle
5 10, 10 20, 20 40, 40 75mg/m²/cycle
PLATINOL PLATINOL-AQ (Bristol Myers)
7.5 75mg/m²/cycle 가 , 5
50mg/m²/cycle 가 , 5
2 4, 4 8, 8 16, 16 35, 35 75mg/m²/cycle P
ARAPLATIN(Bristol Myers) , 7.5 75mg/m²/cycle
가 , 5 50mg/m²/cycle
가 , 2 20mg/m²/cycle
mg/m²/cycle TAXOTERE(Rhone Poulenc Rorer) 30, 30 60
(docetaxel)
10 20, 20 40, 40 70, 70 135mg/kg/cycle
TAXOL (Bristol Myers Squibb) 0.5
5mg/kg/cycle 5- , 2 4, 4
8, 8 15, 15 30, 30 60mg/kg/cycle ADRIAMYCIN(Pharmacia a
mp; Upjohn), DOXIL(Alza), RUBEX(Bristol Myers Squibb)

in vivo

/

가

(humanized) -CTLA-4 MDX-010(Medarex, NJ); RSV
(syncytial) (RSV) SYNAGIS (MedImmune, MD);
-HER2 HERCEPTIN (Trastuzumab)(Genentec)

h, CA)

-CD18 F(ab')₂ (Genentech); -CD18 F(ab')₂ CDP860(Celltech, UK); CD4
 -HIV gp120 PR0542 (Progenics/Genzyme Transgenics); -B
 Ostavar (Protein Design Lab/Novartis); -CMV IgG1 PROTOVIR™ (Protein Design Lab/No
 vartis); -TNF- F(ab')₂ MAK-195(SEGARD)(KnollPharma/BASF); -CD14 IC14(ICOS Ph
 arm); -VEGF IgG1 (Genentech); -CA 125 OVAREX™ (Altarex); -17-I
 A IgG2a PANOREX(Glaxo Wellcome/Centocor); - (GD3) Ig
 G BEC2(ImClone System); -EGFR IgG IMC-C225(ImClone System); - V
 3 (integrin) VITAXIN™ (Applied MolecularEvolution/MedImmune); CD52 IgG1
 Campath1H/LDP-03(Leukosite); -CD33 IgG Smart M195(Protein DesignLab/Kaneb
 o); -CD20 IgG1 RITUXAN™ (IDECPharm/Genentech, Roche/Zettyaku); -CD22 I
 gG LYMPHOCIDE™ (Immunomedics); -HLA Smart ID10(Protein Design Lab);
 -HLA DIAGNOSTIC REAGENT ONCOLYM™ (Lym-1)(Techniclone); -IL8
 ABX-IL8(Abgenix); IgG1 anti-CD11(Genentech/Xoma); ICAM3 ICM3(
 ICOS Pharm); (primatized) -CD80 IDEC-114(IDECPharm/Mitsubishi);
 - -CD20 ZEVALIN™ (IDEC/Schering AG); -CD40L IDEC-131(IDEC/Eisai);
 -CD4 IDEC-151(IDEC); -CD23 IDEC-152(IDEC/Seikagaku);
 -CD3 IgG SMART anti-CD3(Protein Design Lab); - 5(humanized anti-complement fact
 or 5)(C5) 5G1.1(Alexion Pharm); -TNF- D2E7(CAT/BASF); -TNF- Fa
 b CDP870(Celltech); -CD4IgG1 IDEC-151(IDECPharm/SmithKline Beecham);
 -CD4 IgG MDX-CD4(Medarex/Eisai/Genmab); -TNF- CDP571(Celltech);
 - 4 7 LDP-02(LeukoSite/Genentech); -CD4 IgG OrthoClone OKT4A(Or
 tho Biotech); -CD40L IgG ANTOVA™ (Biogen); -VLA-4 IgG ANTEGR
 EN™ (Elan); -CD64 (FcγR) MDX-33(Medarex/Centeon); -IL-5 IgG4 SCH5
 5700(Celltech/Schering); -IL-5 IL-4 SB-240563 SB-240683(SmithKline Beecha
 m); -IgE IgG1 rhuMab-E25(Genentech/Norvartis/Tanox Biosystems); CD-147 IgM
 ABX-CBL(Abgenix); -CD2 IgG BTI-322(Medimmune/Bio Transplant); -CD3 IgG2a
 Orthoclone/OKT3(ortho Biotech); -CD25 IgG1 SIMULECT™ (Novartis Pharm);
 - 2 - IgG LDP-01(LeukoSite); -CD18 F(ab')₂ Anti-LFA-1(Pasteur-Me
 rieux/Immunotech); -TGF- 2 CAT-152(Cambridge Ab Tech); - VII
 Corsevin M(Centocor)

가

()

tease Inhibitor) - (fibronectin) 29kDa N- (kringle) 5, (Serine Pro
 16kDa -4 7.8kDa 40kDa C- (proteolytic)
 13- (Maione et al., 1990, Cancer Res. 51: 2077-2083), I 14-
 (Tolma et al., 1993, J. Cell Biol. 122: 497-511), I 19-
 (Tolsma et al., 1993, J Cell Biol. 122: 497-511), SPARC 20- (Sage
 et al., 1995, J. Cell. Biochem. 57: 1329-1334), (angiogenic)

EGF

(Cao, 1998, Prog Mol Subcell Biol. 20: 161-176). RGD (Arg-Gly-Asp
) (anti-vascularization)
 (Brooks et al., 1994, Science 264: 569-571; Hammes et al., 1996, Nature M
 edicine 2: 529-533). 가,
 (Min et al., 1996, Cancer Res. 56: 2428-33; Crowley et al., 1993, Proc Natl Acad S
 ci. 90: 5021-25).

((LUPRON), LH-RH),
 (dehydrotestosterone),
 ; (antigestagens)(A ((ATRA)); D3

) .
 ,
 -2 가 ,
 (Deshmukh et al., 2001, J Neurosurg. 94: 287-92).

/ DNA / RNA
 , (ribozyme), RNA
 , DNA 가 ,

X- (external-beam) (I-125,)
 (interstitial) , -89 , 가 , P-32 , /

Hellman, Chapter 16: Principles of Cancer Management: Radiation Therapy, 6th edition, 2001, DeVita et al., eds., J.B. Lippencott Company, Philadelphia

(teletherapy)

osensitizer) Pc4, (Vertoporfin(BPD-MA)), (phthalocyanine), (phot
 (demethoxy)- (hypocrellin) A; 2BA-2-DMHA

가 , 가
 가 가 가
 , ()
 (, -)
 , () , ()
) , () , ()

5.18.2

nth) (parasite) , (infectious agent) , (helmi

C.G.A Thomas, Medical Microbiology, Bailliere Tindall, Great Britain 1983
 가

- RNA DNA
 HIV-III) Retroviridae (HIV-1(HTLV-III, LAV HTLV-III/LAV,
 ; HIV-LP (isolates); Picomaviridae (
 , A ;) ; Togaviridae ((equine enceph
 ; Calciviridae () ; Flaviridae () ; Coronavirida
 litis viruses),) ; Rhabdoviridae () ; Filoviridae (
 e () ;) ;) ;)

); *Paramyxoviridae* (); *Orthomyxoviridae* (); *Bungaviridae* (); *Arenaviridae* (); *Reoviridae* (); *Parvoviridae* (); *Papovaviridae* (); *Birnaviridae*; *Hepadnaviridae* (); *Adenoviridae* (); *Herpesviridae* ((HSV) 1 2,); *Poxviridae* (); *Iridoviridae* (); (CMV),); (B (defective satellite), -A, -B (Norwalk)); 1: ; 2: (C); (astroviruses)

B- , C- D- . B- A((rous) (RSV), (MMTV) . C- C- A((AMV)) C- B((ALV), (myeloblastosis) (MSV), (SSV)) (GALV), (MLV), (FeLV), (SNV), (RV) (MPMV) 1(SRV-1) . D- Mason-Pfizer , T- (Visna) , T- (FIV), (EIAV) HIV-1, HIV-2, SIV, (HTLV-1, H (HFV), (STLV), (SFV) (BLV) (BFV)

TLV-II, T- RNA (Orthoreovirus) (), (Orbivirus) ((Bluetongue) , Kemerovo , (Tick)), (), (), Reoviridae ; (), (ME) A B, (ECHO) , A , (Cardiovirus) (), (EMC),), (113 (Aphovirus) ((FMDV)) Pi (N cornaviridae ; , San Miguel , (Semliki) orwalk) Calciviridae ; (), (Chikungunya , O'Nyong-Nyong (Flavivirus) (), (Murray) , Louping III , (Powassan) (tick) , Kyasanur ,), (Bunyavirus) (Bunyamwera , Omsk), (), (), (Sicilian) , Rift (Uukuvirus) (Unkumiemi) Bunyaviridae ; (), A,); C(가) Orthomyxoviridae ; B(), 1, (Morbillivirus) (2 (), (distemper) , (Rinderpest)), ((RSV), , Chikungunya , O'Nyong-Nyong , paramyxoviridae ; , Kyasanur , Louping III , Omsk), (), (), (Bunyamwera , Rift), (), (Crimean-Congo (Uukuniemi) Bunyaviridae ;

(A,), B(), C(가) Orthomyxoviridae ; 2 5, 1, (Rinderpest), (RS V), (Chandipura, Flanders-Hart Park), paramyxoviridae ; (ves iculovirus) (Rhabdovirus)(Marburg), Rhabdoviridae ; (LCM), Tacaribe Arenaviridae ; (IBV), Coronoaviridae . DNA (Ectromelia), (Leporipoxvirus) (가), Poxviridae ; Iridoviridae (2 3, (Lymphocystis)); - (1 2, Varicella-Zoster, 2 3, Herpesviridae ; - (Epstein-Barr (EBV), Marek, Herpes saimiri, (a teles), (sylvilagus), Lucke); (A, B, C, D, E ; (23), Adenoviridae ; 가 ; () , Shope (SV- 40), (RKV), K , BK , JC (Papoviridae ; - , Aleutian DNA Ku ru Creutzfeldt-Jacob .

(AZT, ddI, ddC, 3TC, d4T), - (lopinavir), (amprenavir), (Efavirenz), (Nevirapine), (Kethoxal);

(M. bovis, M. avium, Ad leprae, M. africanum) 가 , Bacillus ant hracis , Erysipelothrix), (Bartonella, Brucella, Campylobacter, Enterobacter, Escherichia, Francisella, Hemophilus, Klebsiella, Morganella, Proteus, Providencia, Pseudomonas, Salmonella, Serratia, Shigella, Vibrio, Yersinia), (spirochete) (Lyme Borrelia burgdorferi), (Actinomyces Clostridium), Streptococcus , Pneumococcus , Staphylococcus , Neisseria , Helicobacterpy

가

V G V G V G V;

B

cryptococcosis), (sporotrichosis), (aspergilliosis), (coccidioidomycosis), (blastomyco-
 sis), (paracoccidioidomycosis), (histoplasmosis), (zygomycosis), (candidiasis)

(), (), (b, (), (), ()

가 B;

(Carbol-Fuchsin);

(ascariasis), (ancylostomiasis), (trichuriasis),

5.19.1 (Effective Dose)

50%가) , LD₅₀ (가 50%) ED₅₀ () , LD₅₀/ED₅₀ 가 , ED₅₀ IC₅₀ (, -)

0.1 , hsp70- / gp96- (combination) 1 60ug
 hsp70- / gp96- 0.1, 0.2, 0.3, 0.5, 0.7, 0.8, 1, 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 550 600ug
 100ug , hsp70- / gp96- 5ug, 25ug, 50ug
 hsp-90 5 5,000ug
 hsp90 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 400, 500, 750, 1000, 1500, 2000, 2500, 3000, 4000 5000ug , 100ug

4-6 , , , , , 가 , , , , , 1 가 4 , 4-6 , 가 가 2 , 가 / , hap- 가 가 , hsp- , hsp- 가 , hsp- 가 , hsp- g, 400-600mg , hsp- GLEEVEC™ (400-800mg) 800mg 400mg GLEEVEC™

hsp- 6 , 6 가 hsp- 1 GLEEVEC™ 2 , 2 1 , 1 1 , 1
 , hsp- GLEEVEC™
 , hsp- GLEEVEC™
 , GLEEVEC™ (400-800mg) hsp-
 2 , 2 1 , 1 1 , 1 6 , 6 , GLEEVEC™ GLEEVEC™
 1 hsp-
 , GLEEVEC™ , hsp-
 () GLEEVEC™
 50mg 100mg, 100mg 200mg, 200mg 300mg, 300mg 400mg, 400mg 500mg, 500mg
 600mg, 600mg 700mg, 700mg 800mg, 800mg 900mg, 900mg 1000mg
 25mg 50mg, 50mg 100mg, 100mg 200mg, 200mg
 300mg, 300mg 400 mg, 400mg 500mg

5.19.2 (Therapeutic Regimens)

-hsp
 -hsp
 1 가 5 , 60 ,
 가
 가
 5.19.1
 1 , 1 2 , 2 3 , 3 4 , 4
 5 , 5 6 , 6 7 , 7 8 , 8 9 , 9 10 , 10
 11 , 11 12 , 24 48
 2 4 , 4 6 , 1 , 1 2 , 2 4 , 1 , 1 2
 (active) 가
 (cycling therap
 y)
 4 6 , 2 4 ,
 1 2
 3 , 2 1 , 10 24

(ADP), gp96

5.19.4

/
 , hsp
 , / hsp 가 , hsp hsp가
 , hsp / 가
 APC,
 , hsp- , hsp- hsp-
 , hsp hsp-
 가 hsp- , 가 , , ,
 hsp- , hsp- 가 (,
 ,), hsp- (needle) ,
 , hsp- /
 hsp-
 hsp- -hsp
 GLEEVECTM , CML, hsp- hsp70-
 (imatinib mesylate)
 , hsp-
 ; hsp- , ,
 -hsp hsp- ; hsp-
 hsp- , , hsp-
 -hsp hsp- ,
 ; hsp- , hs
 p- -hsp hsp- hsp-
 ; hsp- hsp-
 , 가 1 (, ,) /

5.20

) hsp- (hypersensitivity); b) T- *in vitro* ; c) a) 가 (carcinoembryonic, CEA ; d) (CT) ; e) ; f)

5.20.1 (Delayed Hypersensitivity Skin Test)

ery) (anergy) 가 가 (batt (Sato, T., et al, 1995, Clin. Immunol. Pathol., 74: 35-43).
 4
 24 48 . 25- 27- 가 (erythema) (induration)가
 (hypoactivity)

5.20.2 T- *In Vitro*

Ficoll-Hypaque 8x10⁶ T 10%
 3ml RPMI 4x10⁴ C , 33% 2
 IL-2가 T-
 , T- T- 가 , T-
 , W6/32 51Cr- 20% . 6 , 4 51Cr-
 10 12.5% -MHC I (Heike M., et al.,
 J, Immunotherapy, 15: 165-174).

5.20.3

가 , 가
 가 , 가 -
 (oncofetal) 가 ,
 (prototype) 가 ,
 (carcinoembryonic antigen (CEA)) . CEA
 가 가
 가 CEA 가
 (yolk sac)
 (marker) (germinal) 가

5.20.4 (CT)

CT . CT

5.20.5 (putative)

hsp (PSA) Brawer, M.K.,
 et. al., 1992, J. Urol., 147: 841-845, Catalona, W.J., et al., 1993, JA M A, 270: 948-958
 , CEA가
 16 - - Schneider, J.et al., 1982, Proc. Natl. Acad.

Sci. *ISA*, 79: 3047-3051

5.20.6. (sonogram)

가

1 hsp- 가
SEC

2 A 50 60 gp96 30 가 60 가
가 , 30 가

B 50 60 가 gp96 NECA 60 가 가
, 30 gp96 NECA

C D gp96 50 60 30 가 MCP-1 NO APC gp96

E F gp96 NECA pH
NECA pH 3.0

G H APC MCP-1 NO gp96 pH
MCP-1 NO pH 3.0

3 gp96 SEC . 8 - 10 hsp-

4 gp96 SEC . 8 - 10 hsp-

5 3 4 SDS-PAGE . 2-5 gp96
8 - 10

6 3-5 ATPase 8 - 10 가 ATPase
가 , (2-5) (11-15) ATPase

7 AH1 19 (mer) gp96 gp96 AH1 19 IFN-
가 APCs CTLs IFN-
APCs CTLs

MHC 1 AH1 9 gp96 AH1 19 gp96/AHI I9 10µg/ml
(unloaded) gp96 1:3, 1:10 1:30

IFN- (unloaded) gp96

AH1 19 - gp96

60 10 가 T-

8 gp96 10 % ATPase

ATPase

가

in vitro _____

(aliquot) 4 (Gp96- CT-26)

1 SEC

가 3 IFN- 가 2 T- 가

[2]

	SEC	%	NECA (ug NECA gp96/ug gp96)	T- (IFN-) (pg/ml)
1				
4	75.8		3.27	102600
60 , 60	0		0.08	9350
60 , 120	0		0.10	8100
2				
4	84.44		1.68	19600
49.5 , 30	0		0.12	3150
60 , 30	0		0.04	50
3				
4	87		1.96	8000
49 , 15	74		1.97	0
49 , 25	54		1.80	0
60 , 30	0		0.07	0

NECA gp96 CT-26 gp96-

2 NECA , NECA 3

(antigen presenting cell) /

gp96 가 Meth-A gp96 pH

SEC NECA 가 MCP-1 2 gp96

MCP-1 NO NECA

pH 7 9 gp96 pH 3

ATPase _____

gp96 ATPase (mg ATP 가)

gp96 (isoform) ATPase 가 gp96-
 가 (3-6) gp96-
 3 SEC ()

5 SEC SDS-PAGE 96kDa
 SEC

2-5 , 8-10 11 12 SDS-PAGE
 13

ATPase mg ATP 가 (luminescence) ATP
 ATPase . ATPase 6
 , gp96가 ATP 가

gp96-
 gp96- 가 ATPase
 gp96 (-)

ATPase

가 ATPase ATPase gp96 , -
 gp96 - gp96 ATPase

CD8 T-)가 hsp *in vitro* , AH1 (. gp96-
 T- ATPase S

EC % hsp hsp- , ATPase

gp96 ()
 homogenized), , 50%
 Con A DEAE -80

(RAW264.7(ATCC#TIB-71)) Abelson
 BALB/c (H-2^d) CT26 AH1 CTL P. Sri
 vastava(U. of Conn. Medical Center) AH1 가 BALB/c (s
 plenocyte) - 9 AH1 (SPSYVYHQF)
 19mer (RVTYHSPSYVYHQFERRAK)가 Sigma Genosys 1442 lake Front Circle, The Woodlands,
 Texas 77380-3600

AH1 19mer gp96 50:1 37
 30 30K MWCO Centricon (Millipore)
 10 PBS 가 4 Bradford

in vitro - , 10⁴ AH1 - CTL(8) 96-
 10⁴ RAW264.7 - . 10ug/ml *in vitro* gp96
 37 18 , IFN- ELISA(

Ramp;D Systems) 6 AH1 9mer
 가 gp96, AH 19mer CTL APC
 ATPase 가 mg ATP 가 37 4 ATP hap90
 (geldanamycin)
 mM MgCl₂ 400M gp96 (2uL, 500ug/mL in PBS) 10 ATP PBS (12.5
 37 4 20%(v/v) DMSO DMSO) 2uL
 PBS 가 100ul 50ul
 ATP ROCHE CLSII bioluminescence ATP (Bioluminesc
 ence) Molecular Devices Lmax 가
 가 ATP gp96 ATP 가 mg
 가 ATP nmole
 HPLC 가 10m
 M , pH 7.1(300mM NaCl) TSK 3000SWXL (Toso Haus) Superose 6 (Amersha
 m Pharmacia) , Waters Alliance HP1100 HPLC
 , 0.5 mL/min gp96(3) Superose 6
 .%

[3]

			ATPase (Nmol/mg/hr)		%		
			가	가	가	가	
1	10-12-01	(10-10-01)		8.5 ± 0.3	0	86	0
2	10-19-01	(10-10-01)		9.4 ± 0.5	0	83	0
3	10-19-01	(10-17-01)		10.3 ± 0.1	0	84	0

3 gp96 , ATPase
 % gp96 AH1 19mer 60 10 가 , IFN-
 가 IFN-
 10 60
 T- APC
 gp96 AH1 19mer 7 gp96 APC CTL IFN-
 CTL APC
 9mer gp96 AH1 19mer MHC I 가 AH1
 96 1:3, 1:10 1:30 . gp96/AH1 19mer 10ug/mL gp
 IFN- gp96
 AH1 19mer- gp96 10 60 가 , T-
 가

gp96 가 ,
 T- 가 .
 3 gp96- ATPase %가 SEC
 ATPase , ATPase ATPase 가 , SEC
 ATPase , SEC 가 *in vitro*
 가

ATPase (ATPASE ACTIVITY IS STABILITY INDICATING)

ATPase - . gp96 가
 ATPase , . gp96
 SEC ATPase %가 8 gp96 10
 ATPsse gp96 가
 gp96- ATPase ,
 가 가
 가

(57)

1. (ATPase) (AT
2. gp96- gp96- (ATPase)
- 3.
4. gp96- gp96-
5. (a) (ATPase) ;
 (b) ;
 (c) (ATPase) ATPase ;
 (d) (ATPase) (ATPase)

- 5 **6.** , (ATPase) , HPLC, (immunoaffinity) .
- 5 **7.** , - hsp (ATPase) (ATPase) , .
- 7 **8.** , -hsp (geldanamycin) NECA .
- 5 **9.** , - (specific activity) , .
- (a) **10.** - ;
- (b) - ;
- (c) - ;
- (d) - .
- 10 **11.** , - , , , , .
- se) **12.** - (ATPase) (subject) - (ATPase) (ATPa) , .
- 13.** - (ATPase) (subject) - (ATPase) .
- 5 **14.** , 10 , 12 13 , hsp- hsp gp96 .
- ase) **15.** 1 , 2 , 12 13 , - (ATP) .
- 16.**

- 15 (immunoaffinity) (ATPase)
17.
3, 4, 12 13
- 18.
- 17
19.
15 - hsp (ATPase) (ATPase)
20.
19 - hsp (geldanamycin) NECA
21.
15 (specific activity)
22.
12 13
23.
Pase) (instruction) (ATPase) (AT
24.
1, 2, 3, 4, 5, 10, 12 13
25.
24 (representation) T-
- 26.
- 23
27.
23 (representation) T-
28.
1, 2, 3, 4, 5, 10, 12 13
, MCP-1, CD91 CD36
29.
23 ; MCP-1 ; CD
91 CD36

30. 1, 3, 5, 10, 12, 13, hsp- hsp hsp 70, hsp 90 hsp 60 hsp
31. 23, hsp- hsp hsp 70, hsp 90 hsp 60 hsp
32. 1, 3, 5, 10, 12, 13, hsp- hsp hsp 90, gp 96(gp 94), hsp 104, hsp 70 hsp 60 hsp
33. 23, hsp- hsp hsp 90, gp 96(gp94), hsp 104, hsp 70 hsp 60 hsp
34. 가, 4,4'- (dianilino)-1,1'- (binaphthyl)-5, 5' (disulfonic) ('bis-ANS'), (hexanoate; SASD) (sulfosuccinimidyl) [4- (azidosalicyla mido)] 가
35. 가 bis-ANS, SASD가 가
36. 34, .
37. 34 35, gp96 hsp 90 .
38. 34 35, .
39. 26, .
40. 가, bis-ANS, SASD가 가 가 가
41. 가 bis-ANS, SASD가 가 가 가
42. 40 41, gp96 hsp 90 .
- 43.

40 41 ,

43 44. ,

45. 가 , bis-ANS, SASD가
가

46. 가 bis-ANS, SASD가
가

47. 가

45 , 46 47 , gp96 hsp 90

45 , 46 47 ,

45 , 46 47 ,

51 51. ,

52. 가 , bis-ANS, SASD가

53. 가 bis-ANS, SASD가

52 53 , gp96 hsp 90

52 55. 53 ,

55 56. ,

56 57.

58.

가 , bis-ANS, SASD가
가

59.

가

58 60. 59

58 61. 59

58 62. 59

58 63. 59

58 64. 59

gp96 hsp 90

65.

가 , bis-ANS, SASD가 가 -

66.

가

65 67. 66

gp96 hsp 90

65 68. 66

68 69.

68 70.

71.

가 , bis-ANS,

SASD가

가

-

가

72.

,

가

-

가

73.

71

72

,

gp96

hsp 90

.

74.

71

72

,

75.

74

,

76.

74

,

77.

(a)

가

, bis-ANS,

SASD가

;

(b)

가

78.

(a)

가 bis-ANS,

SASD가

가

,

;

(b)

가

79.

77

78

,

80.

79

,

81.

77

78

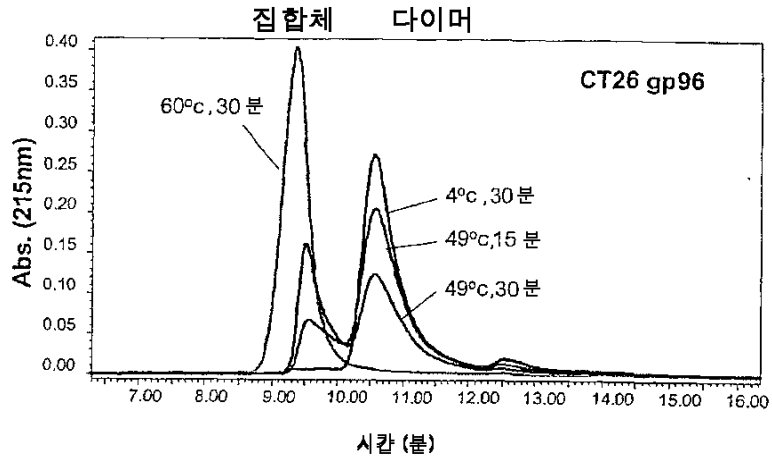
,

gp96

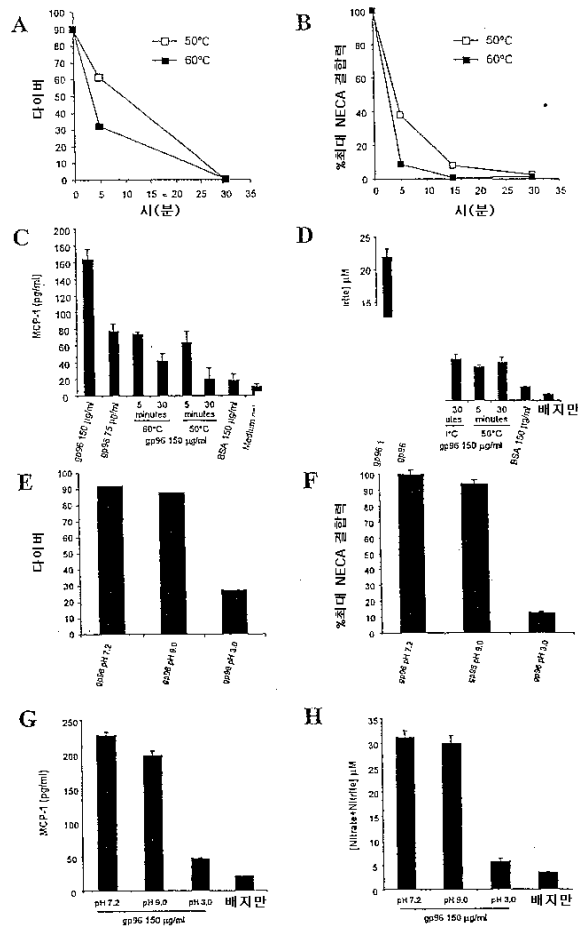
hsp 90

.

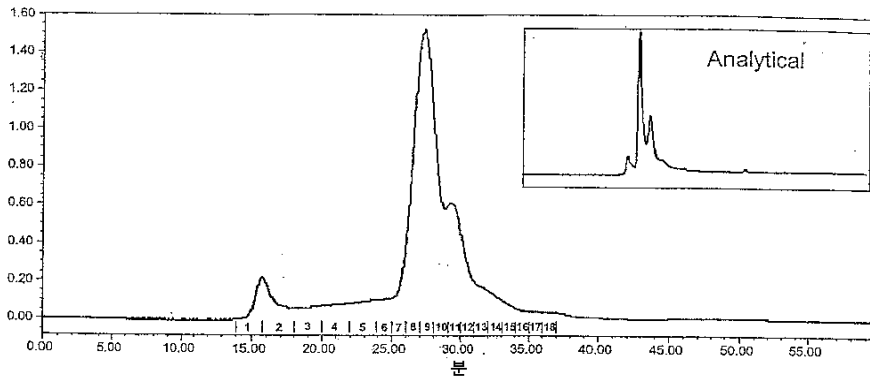
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2

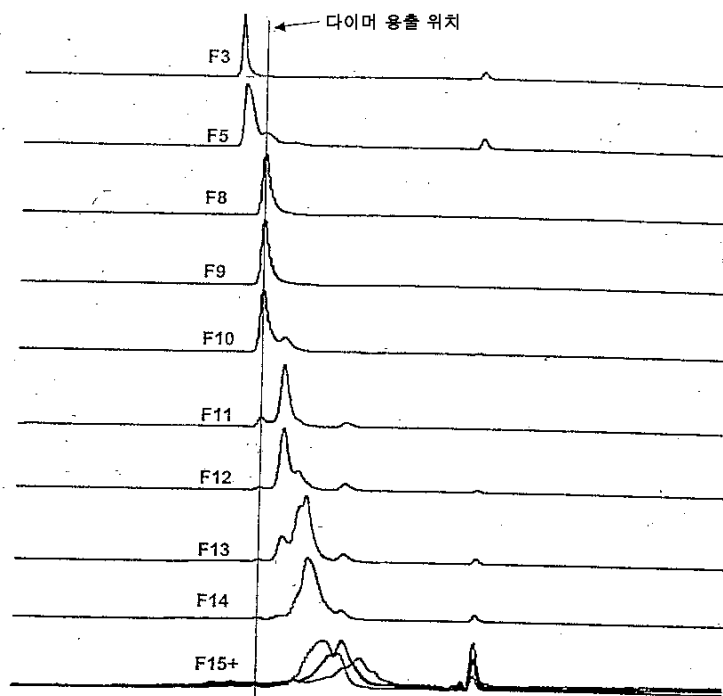


3

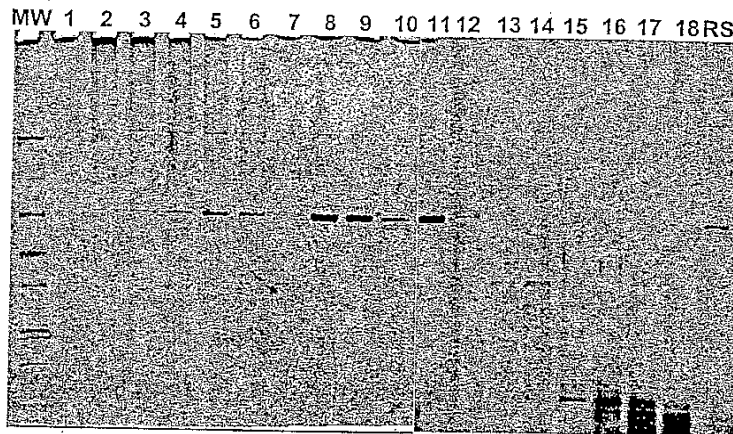


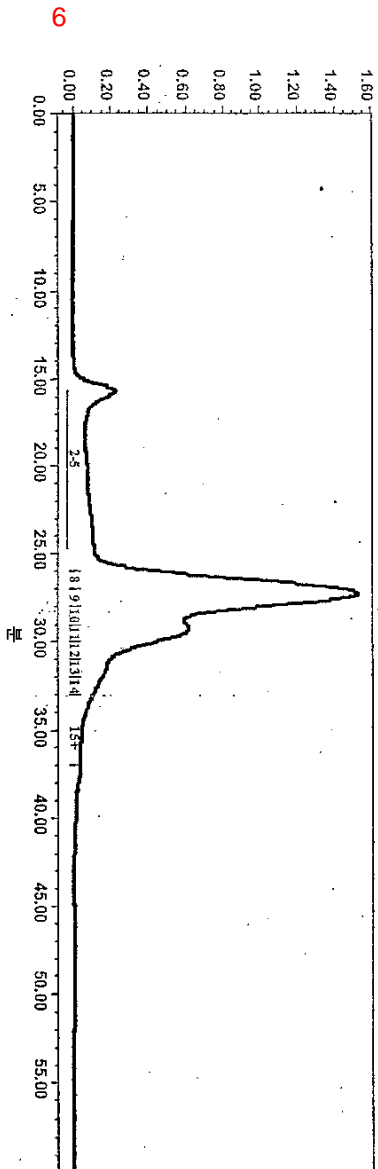
4

Analytical SEC of
Superose 6
column fractions

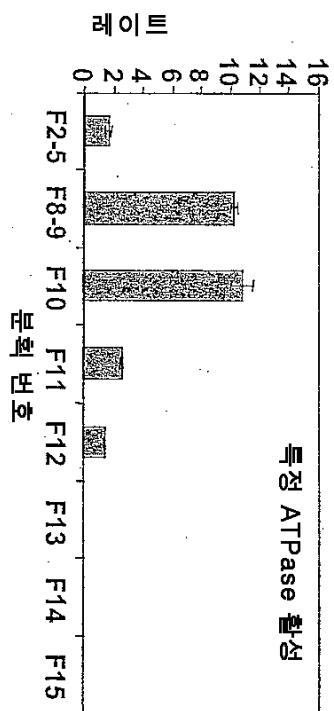


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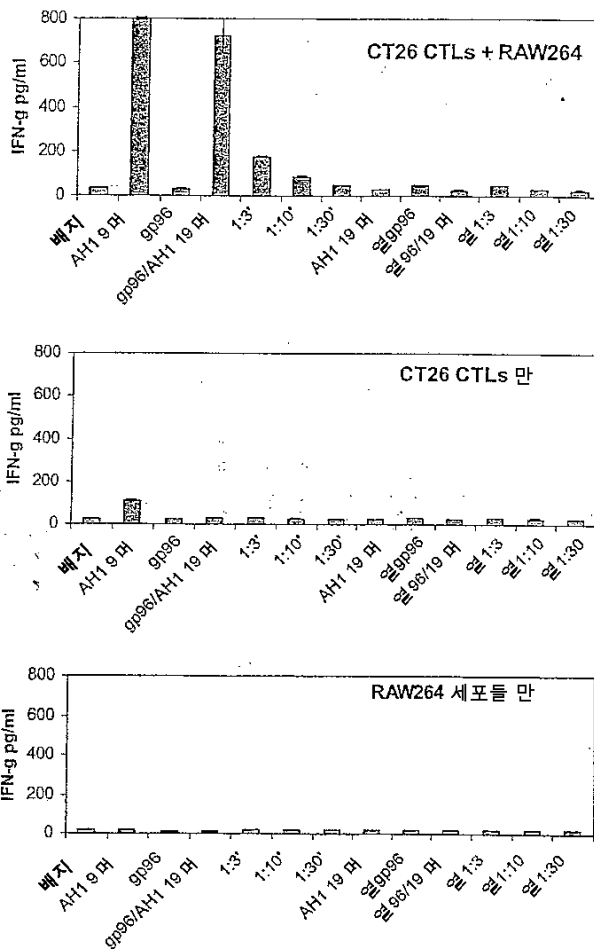




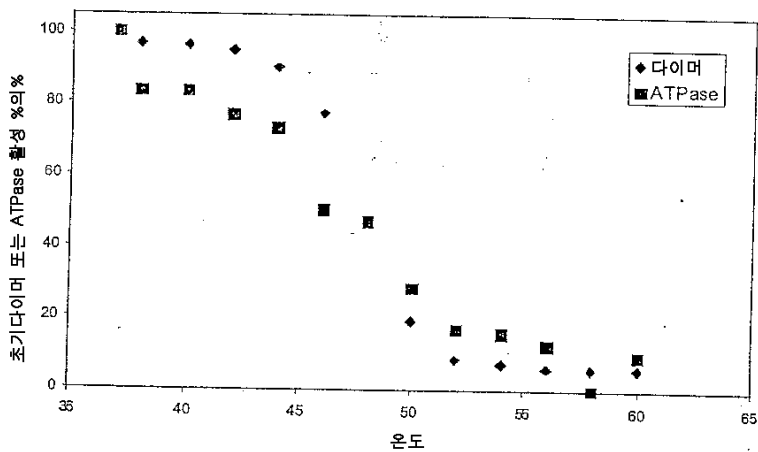
9



7



8



<110> ANTIGENIC INC.

UNIVERSITY OF CONNECTICUT HEALTH CENTER

<120> METHODS AND PRODUCTS BASED ON OLIGOMERIZATION OF STRESS PROTEINS

<150> US60/361257

<151> 2002-02-28

<160> 2

<170> KopatentIn 1.71

<210> 1

<211> 9

<212> PRT

<213> Murine leukemia virus

<400> 1

Ser Pro Ser Tyr Val Tyr His Gln Phe

1 5

<210> 2

<211> 19

<212> PRT

<213> Murine leukemia virus

<400> 2

Arg Val Thr Tyr His Ser Pro Ser Tyr Val Tyr His Gln Phe Glu Arg

1 5 10 15

Arg Ala Lys