

(19) (KR)
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(30) 09/893,344 2001 06 28 (US)

(71) 76100 . . . 95

(72) -
76353 5

76880 94

76388 16

(74)
:

(54) - G L U , T Y R , T

(a) -Glu,Tyr, (b) -Glu,Tyr T , (CN
S) (PNS) ,
CNS .

2

(NS) , , (CNS)
, , CNS (PNS)

CNS , CNS
 가 , , 가 (, 3 4 - 2
) 가 가 , 가 (, 3 4 - 2
)
 , N- (AMPA)- -D- 가 (NMDA)- CNS -3- -5- -4- NMDA AMPA NMDA
 , NMDA AMPA MK801
 , NMDA AMPA (Meldrum, 2000).
 , US 09/218,277 , NS 09/314,161, PCT WO 99/60021 ((partially crushed
 optic nerve) (Moalem , 1999) , MBP T 가 (Hauben , 2000)) , CNS
 T 가 CNS PNS NS T 2
 , CNS T NS T 가
 (Hirshbeg , 1998).
 NS T , US PCT WO 99/60021 , NS , Thy-1, P0, P2
 , odenrocyte) , (MOG) MBP, MAG, S-100, - (PLP), (olig
 51-70 MOG 35-55 NS , MPB
 0.338 L-Ala, L-Glu, L-Lys L-Tyr (0.141, 0.427, 0.095
 , COPAXONE[®] (Teva Pharmaceuticals Ltd., Israel)) , CNS PNS Cop 1
 WO 01/93893 US 09/487,793, 09/620,216 09/765,644, PCT WO 01/52878
 T ((非) , 2) , Cop 1
 P 359 783 가 가 , PCT WO 91/12816, WO 91/0
 8760 WO 92/06704 MBP 가 T 1
 PCT WO 98/30227
 GT , 100 pEY , -Glu⁵⁰ Tyr⁵⁰ L- L-
 (inbred) (Vidovic , 1985; Vidvic Matzinger, 1988). 20 , pEY
 pEY (congenic resistant) , (MBSA)
 pEY-MBSA - (PFC) 가 ; pEY
 pEY

(Debre , 1975). (Seo , 2001). , pEY V (syngeneic recipient) 5/V 1-TCR(+) T pEY , 가 .

sion) 2 -Glu,Tyr T -Glu,Tyr T- 가 MBP T (contu -Glu,Tyr .

T , 가 (a) -Glu,Tyr (b) -Glu,Tyr .

-Glu,Tyr T (autologous) T (semi-allogeneic) T -Glu,Tyr (donor) HLA T 가 .

(axon) , CNS PNS , CNS PNS , CNS PNS , (coup) (contrecoup) , (ALS), , (macular) .

T , (a) -Glu,Tyr (b) -Glu,Tyr .

-Glu,Tyr CNS PNS CNS PNS T CNS PNS (a) -Glu,Tyr (b)

1 CNS PNS , 2
 가
 T , (i) -Glu,Tyr T T , (ii) T
 -Glu,Tyr -Glu,Tyr -Glu,Tyr
 T 1 NS 2
 -Glu,Tyr T , () ()
 1 2 -Glu,Tyr T 1 2
 , -Glu,Tyr 가 , -Glu,Tyr -Glu,Tyr
 T 가
 u,Tyr , T CNS PNS , -GI
 , -Glu,Tyr T
 -Glu,Tyr (ajuvant) -Glu,Tyr 1
 , T (boost) , T -Glu,Tyr
 , T , 가 (MHC)- T II
 MHC II , T 가 , T 가
 , -Glu,Tyr
 A, -Glu,Tyr (PHA) (mitogen),
 1

1 : (Ova),
 1 (Cop 1), (MBP), MBP p87-99, -Glu,Tyr (pEY) (concanavalin)
 A (Con A). SPD 8-10

(SI = 1)

2 pEY 가 (RGC) (CFA-pEY) CFA PBS (C
 AF-PBS) C57BL/6J (naive) RGC /mm² ± 7
 3 pEY/CFA () CFA-PBS (hindlimb) ; pEY/CFA () SPD BBB () ±
 4 ; ; pEY CFA-pEY SPD T (SPc + pEY; (adoptive transfer) CFA-PBS T (hindlimb)
 ±

-Glu,Tyr T T , NS CNS , -Glu,Tyr CNS PNS T
 , NS, CNS , T CNS
 -Glu,Tyr T (同氣), T , HLA CD4 / CD8 -
 T T , T
 , T 1-3 CNS T
 - T , MHC (APC)가 T MHC (I II) , T
 MHC T (APC) HLA-DR HLA-DQ HLA ,
 yr -Glu,Tyr T - NS 가 -Glu,T
 , T (migration) CNS
 - T , 가 T 2 2 가 가
 .2 , - T , T , T
 , HLA II HLA-DR5 , HLA-DR5 , -Glu,Tyr
 T HLA-DR5 50% 가 T 가 HLA ,
 DR1, DR4, DR2 T , T
 T T T

-Glu,Tyr T , -Glu,Tyr T 가 ,
 4 (Cohen) : T 1.5-10.0 Rads (Ben-Nun , 1982); / U.S. 4,996,19
 T -Glu,Tyr T
 3.2 (Mor , 1995) T
 -Glu,Tyr T 가 , -Glu,Tyr
 T (, Pette , 1990,
 T , T 가 (TNF-),
 -2 (IL-2) -4 (IL-4) , NS
 4/5 (NT- 4/5), : T - (TNF-), (NGF), 3 (NT-3),
 (BDNF); - (IFN-) -6 (IL-6).
 T -Glu,Tyr T
 -Glu,Tyr T , T (PBL)
 -Glu,Tyr T
 , i- (DMSO), , D- , D- , D- , i- , D-
 DMSO
 가 (bath) 가
 가 Cryomed 가 Planar
 80 -20 (Thermos)
 (-196) 가

-Glu,Tyr

T

가

()

가

-Glu,Tyr

T

가

T

T

가

(monochydrate);

l), 가,)

(intranasa

가 가

가

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가(buccal)

(lozenge)

-Glu,Tyr

가

(bolus)

(injection)

(infusion)

가

(retention)

가

가

가

(吹入器)

-Glu,Tyr

(nose drop)

-Glu,Tyr (trachea)

-Glu,Tyr -Glu,Tyr T
(lignocaine) 가

-Glu,Tyr

Intralipid Lipofundin (alum) 가
-Glu,Tyr WO 97/02016 (TH1 TH2 TH2) 가

, NS

-Glu,Tyr -Glu,Tyr T
-Glu,Tyr -Glu,Tyr

T

1220, US 5,800,812, US 6,117,424 US 6,267,955 (: (a) (WO 97/09985, WO 98/4
) (phagocyte),) (mo
nocyte); (b)

, WO 97/09985, WO 98/41220, US 5,800,812, US 6,117,424 US 6,267,955 , CNS
-Glu,Tyr -Glu,Tyr T

2 , 1 -Glu,Tyr -Glu,Tyr T
1 , 1/4 1 , 6 1
CNS 가 , 2

(, ,), , 가

-Glu,Tyr T NS
10⁵ , 5 x 10⁶ 10⁷
10⁷ 10⁸ 10⁶ - 10⁷ , T
가

2 , -Glu,Tyr T
(window of opportunity)가
1 가 , 1-2

, NS 2
 T
 , -Glu,Tyr
 ,
 , CNS 가 , NS
 , T MHC II 가 ,
 T
 Institutional Animal Care and Use Committee (IACUC)
 8-13 C57BL/6J 8-12 SPD Animal Breeding Center of the
 Weizmann Institute of Science (Rehovot, Israel) (ketamine) 80 mg/kg (xylazine
) 16 mg/kg
 (guinea pig) MBP, (OVA), -Glu,Tyr Con-A Sigma (St. Louis,
 MO) Cop 1 Teva Pharmaceuticals (Petah Tikva, Israel) MBP p87-99
 Weizmann Institute of Science (Rehovot, Israel)
 0.5 mg/ml CFA
 100 µg -Glu,Tyr (0.1 ml)
 CFA (Difco, Detroit, Michigan, USA) PBS
 (sclera) 27-
 , 30- 10 µl Hamilton
 1 µl (200 nmol) L-
 T T (draining lymph node)
 (Ben-Nun , 1981). PBS (1 mg/ml) , 4 mg/ml
 (Difco) (IFA) (Difco Laboratories, Detroit, MI)
 . 0.1 ml 10
 , L- (2 mM), 2- (5 × 10⁻⁵ M),
 (1 mM), (100 IU/ml), (100 µg/ml), (1 ml/100 ml)
 1% (/) Dulbecco's modified Eagle's (DMEM)
 (10 µg/ml) . 37 72 , 98% 10% CO₂ 72
 , DMEM, L- , 2-
 (10% (FCS) (/), A (ConA)
 , 10% T- (2000 rad) (10⁷ /ml) (10 µg/ml) . T
 (Ben-Nun , 1982).
 : (a) Rompun (10 mg/kg; Vitamed, I
 srael) Vetalar (50 mg/kg; Fort Dodge Laboratories, Fort Dodge, LA) (i.p.)
 (conjunctiva)
 (intraorbital)
 (calibrated cross-action forcep) 1-2 mm
 (2) 가 2
 (Yoles, 1998).
 ; (b) 1-

2 mm
)
 RGC 2
))-N- (4-Di-10-Asp) (Molecular Probes Europe BV, Netherlands)
 가 , 2 가 가 1 2 가
 가 RGC
 m (axotomy) 1-2 m
 4-Di-10-Asp (0.2 - 0.4 mm)
 5 , 4%
 RGC
 (RCG) . RCG 72
 (stereotactic) , 가 2 mm , 2.92 m
 m , 0.5 mm
 FluoroGold (5% ; Fluorochrome, Denver, CO) Hamilton
 (1 μℓ, 0.5 μℓ/) ,
 RGC 가. (170 mg/kg)
 mm²) 4-6 (PBS 4%) (0.7
 (, ×800) , 가 (optic disk)
 RGC RGC
 4-(4-())-N- (4-Di-10-Asp) (Molecular Probes Europe BV, Neth
 erlans)
 1-2 mm , 4-Di-10-Asp
 (0.2-0.4 mm) 5 , RGC
 , 40% , (DTMR) (Mole
 IOP , 3000 MW DTMR 2 3 mm
 cular Probes, OR) . 24 가 , 8 2
 (가 0.66 1.103 mm) 400x
 , 7 , (170 mg/kg)
 10 μm) , (PBS 4%) 48 4 (Hamp;E)
 mg/kg), (0.3 mg/kg) Lewis (15 mg/kg), (1.5
 al veins) (IOP) 가 (limbal) (episcler
 130-150 ; Coherent, Palo Alto, CA) 1 2 (0.2 1 watt, 2 50 μm
 3.0 mg/kg , TONO-PEN (Mentor, Norwell, MA) IOP 0.5%
 1. T-
 SPD , T8 (laminectomy) 1

, 10 g (rod) NYU (Basso, 1995, 1996) 50 mm

8-10 (2 × 10⁶ /Mℓ), (1 mM), (100 IU/Mℓ), (2 mM), 2- (5 × 10⁻⁵)

M), 1% (/) (15 μg/Mℓ) Con A (1.25 μg/Mℓ) (100 μg/Mℓ), (2000 rad, 2 × 10⁶)

/Mℓ) DMEM 0.2 Mℓ 3 [³H] (1 μCi/) (SI) (72 Ova, Cop 1,)

MBP, 87-99, -Glu,Tyr Con A , [³H] (1 μCi/) (SI) (72 Ova, Cop 1,)

16 가) (SI = 1)

Cop-1 T- MBP Con-A -Glu,Tyr T- 1 가

2.

-Glu,Tyr

C57B1/6J , RGC 가 (24),

Glu,Tyr , 8 C57B1/6J , 7 CFA CFA 100 μg - PBS

7 , RGC

-Glu,Tyr , PBS mm² RGC 2796 ± 165, 2874 ± 197 2807 ± 42 mm² RGC

, 100% RGC (0%)

2 (t - , p = 0.01) GFA -Glu,Tyr (CFA-EY) 가 PBS (t - , p = 0.0

07) . 2 RGC (t - , p = 0.71).

3.

12

-Glu,Tyr

3.1 -Glu,Tyr : -Glu,Tyr/CFA

NYU 50 mm 10 g T8 NYU 12 SPD

PBS/CFA () SC . 2 (6)
 , 7 , pEY/CFA (100 µg/ 2 ,) SC
 Basso (1995) ()
 Basso, Beattie, Bresnahan (BBB) Locomotor rating Scale (0 21) ,
 , 가 . 3 , pEY () (90 cm, 7 cm) 4
 가 PBS

3.2 -Glu,Tyr

-Glu,Tyr T 가 ,
 T , 4 SPD pEY/CFA (125 µg/Mℓ) SC . 7 ,
 S , pEY (10 µg/Mℓ) 3 , PB
 12 SPD , 3.1 , 50 mm
 10 g T7 , 0.5 Mℓ PBS , pEY (30 × 10⁶ /0.5 Mℓ PBS
 /) , BBB
 4 , pEY () 가 ()

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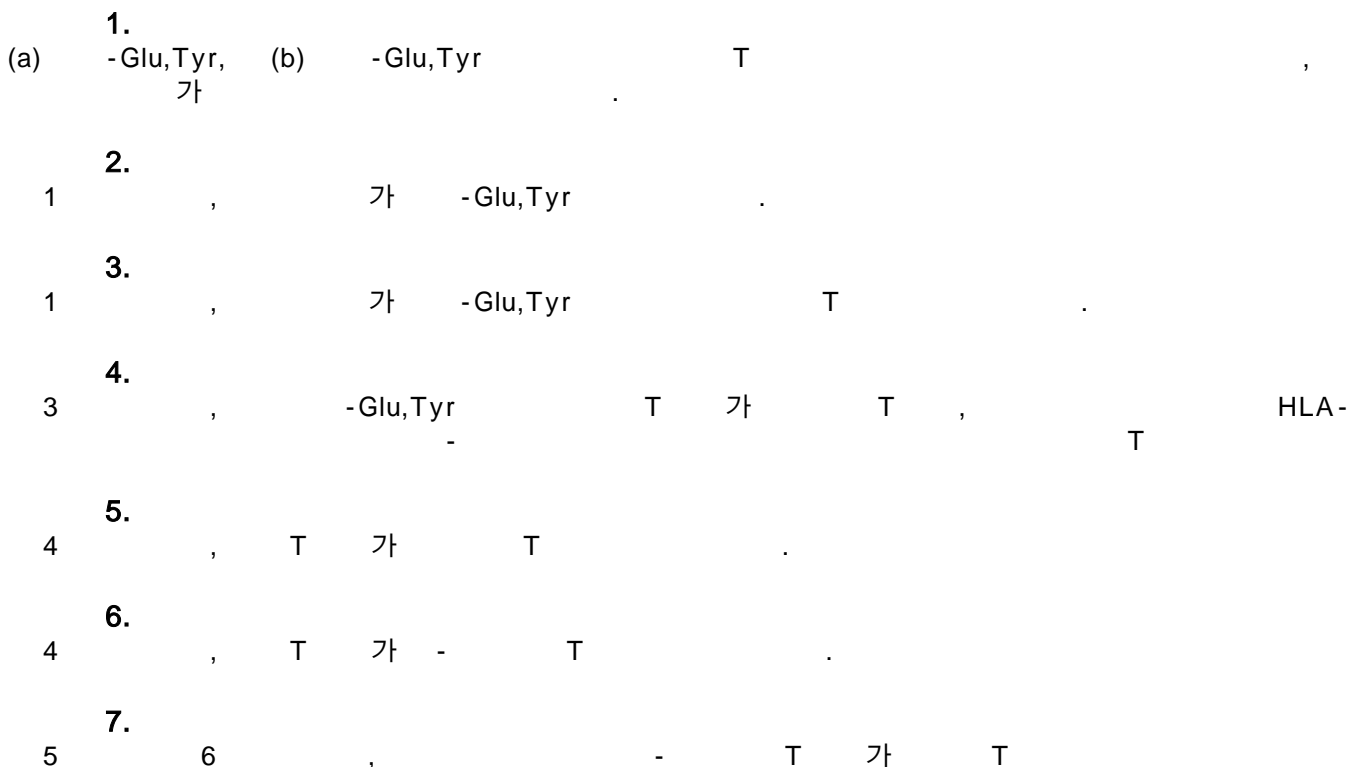
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(57)



(adrenomyeloneuropathy),
(Refsum's disease),

(giant axonal neuropathy),

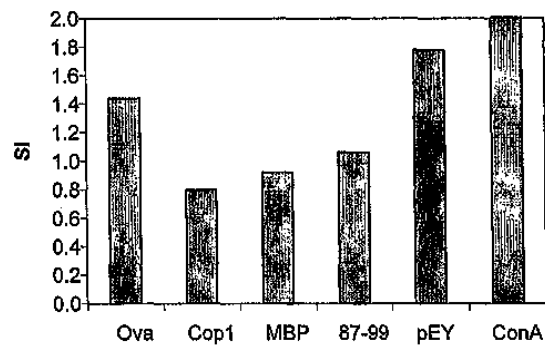
29.

25

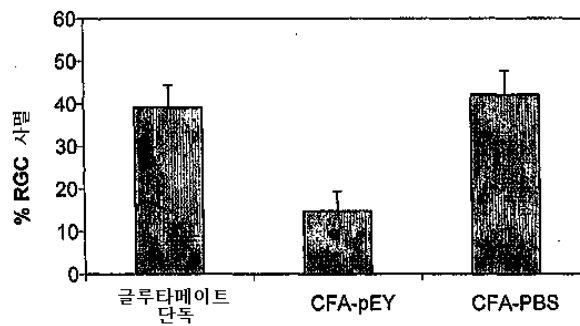
30.

28

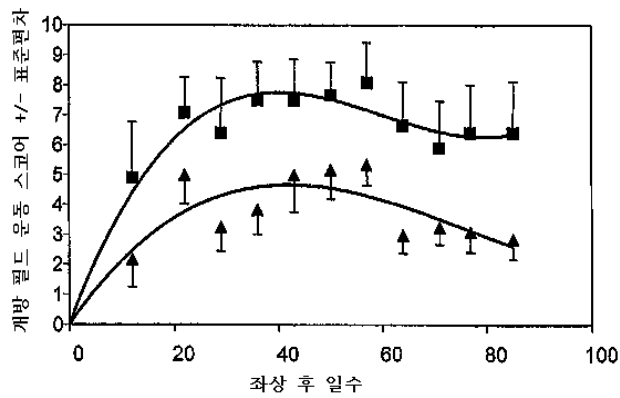
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