

(19) (KR)
(12) (B1)

(51) . Int. Cl.6 (45) 2003 12 18
A61K 38/41 (11) 10-0399501
 (24) 2003 09 16

(21)	10-1998-0709026	(65)	2000-0010882
(22)	1998 11 09	(43)	2000 02 25
	1998 11 09		
(86)	PCT/IB1997/00489	(87)	WO 1997/41883
(86)	1997 05 05	(87)	1997 11 13

(30) PN 9765 1996 05 09 (AU)

(73) - - 376 6002

(72) - 75005

(74)

(54)

가 , , , ,

- (IFN- γ) , , AIDS- (Kaposi)
 [(Gutterman J.U) ' Proc. Natl. Acad. Sci. USA ', 1994 91 :1198-1205].
 - (IFN- γ) B 가 |
 . - - - | . , , ,
 . 가 | ,

(Cantell) (Phyhalo) ' *J. Gen. Virol.* ' 1973 **20** :97-104; (Wills) ' *J. IFN Res.* ', 1985 **5** ;403-408 [].
 984 **4** :399-409; (Gilson) ' *J. IFN Res.* ', 1985 **5** ;403-408 [].
 (*Plasmodium berghei*)
 (Sporozoite)
 [(Jahiel) ' *Science* ', 1986 **16**: 1802; ' *Nature* ', 1968 **220** :
 710; ' *Amer. J. Trop. Med. Hyg.* ', 1969 **18** : 823]. (Newcastle)

pre)- (phase) (, 3 40) ['Nature' 1970 **227** : 1350-1351].

[(Hayden) 'J. Infect.
' New Engl. J. Med', 1986 [
' New Engl. J. Med', 1986 - 2
[(Douglas) ' New Engl. J. Med', 1986
314 : 65-80;
314 : 71-75]
가

19 , 583332 (theileriosis) (5,215,741 4,462,985).
 1 0.01 5IU

[(Bocci) ' *Clin. Pharmacokinet.* ', 1991, **21** :411-417; ' *Critic, Rev. Therap. Drug Carrier Systems* ', 1992, **9** :91-133; (Cummins) (Georgiades) ' *Archivum Immun. Therap. Exper.* ', 1993, **41** :169-172]. [(Kaiser) ' *AIDS* ' 1992 **6** :563-569; (Koech) ' *Mol. Biol. Ther.* ', 1990 **2** :91-95]. HIV, AIDS, B

[(Zielinska) 'Archiv. Immunol. Therap. Exp.', 1993, 41:241-252].
, (Brigham) WO95/27499 (Women's Hospital)
,
가
(bystander)'
가]

가 , , , , - (Creutzfeldt-Jakob syndrome) , , , , B , C , (human immunodeficiency virus: HIV), (herpes simplex virus: HSV)-1 HSV-2 (human papilloma virus: HPV),

IU 1 20×10^6 IU, 1500IU, 가 5000IU, 20×10^6 IU, 1 1×10^4 , 1 1×10^4

, 1500IU, 5000IU, 20×10^6 IU, 1×10^4 IU
 20×10^6 IU, 가 1×10^4 IU 1×10^6 IU

IFN-
IFN-

(, 5,582,824 , 5,593,667 5,594,107) , 가

가

가 , 가 (Tilorone)[3592819 ; (Albrecht)
 ' J. Med. Chem. ', 1974, 17 :1150-1156]
 (Imiquimod)[(Savage)
 ' Brit. J. Cancer ', 1996, 74 :1482-1486]가

, CMV, HIV, HPV, HSV I II ; AIDS HIV . B C

2 , , I II (*Plasmodium malariae*), (*Plasmodium vivax*),
(*Plasmodium falciparum*) (*Plasmodium ovale*) .

3 , HIV. , AIDS

가 . HIV (protease) 가 () HIV
/ HIV , IFN 가 ,
, IFN [(Remington), 'The Science and Practice of Phar
macy, 19 , Mack Publishing Co, Easton, PA, 1995] . IFN
4,496,537 , /

IFN IFN IFN IFN

，，，，，，**(頰側)**，
가

가

BP 45%; BP 30%; BP 11%; BP 5%; BPC 4%;
 USP 3%; BP 2%; 10^6 IU IFN-2

(pH 4.5) 25%, 100%가 4,675,184 10⁻⁶ IU IFN-₂ 45%, CMC 2%, .

, 가 가

가

각각의 허리에 걸친 체인은 그녀의 몸을 끌어당기고 그녀의 손과 발을 묶어버렸다.

가 , 가

00IU 20×10⁶ IU 1×10⁴ IU 1×10⁴ IU, 20×10⁶ IU, 가 1500IU, 50

가

IFN- /							
IFN- / (Mu IFN- /)							
10 ⁶ (IU)/Mℓ 가 1mg 5×10 ⁷ IU (VSV) (NIH) 가 (IFN- /							
929 4x ' Proc. Soc. Exp. Biol. and Med.', 1974 146 :809-815							
9004-5411) .							
IFN- 1-8							
IFN- 1-8 [Hu IFN- 1-8; BDBB -Geigy)] 86 67 :1633-1643].							
457) VSV WISH 1×10 ⁶ IU/Mℓ 가 가 . NIH 70×10 ⁶ IU/Mℓ 가 가 , IFN- . IFN 1mg 2×10 ⁸ IU .							
929 ' J. Gen. Virol.', 1977 267:455- L929 NIH IFN 'Nature', 1977 267:455- .							
46:406-415). .							
6×10 ⁶ IU/							
Me 가 1mg 6×10 ⁸ IU (Life Technologies Inc.)							
Me 가 1mg 8×10 ⁶ IU (Ramp;D Systems Inc.)							
46:406-415). L929 3.2×10 ⁴ IU/							
2580-03SA) VSV 1×10 ⁷ IU 가 (' Proc. Soc. Exp. Biol. Med.', 1974, 1 146:406-415). /							
(G-002-9004-5411) / (Ferimmune,)							
IA ; ; (BSA) A7888; (Sigma) PBS(pH 7.4) 1Mℓ 100μg V[R							
1 ; , , (Pharma Pacific)]:							

	/ %	mg/
()BP **	44.67 ***	55.84
BP **	30.06	37.58
BP **	11.31	14.14
BP **	4.96	6.20
BPC **	4.03	5.04
USP	3.00	3.75
BP	1.88	2.35
40 ** (40 BP)	0.06	0.08
BP	0.03	0.04
BP	0.01	0.01
BP	0.01	0.01
	100.02	125.04

2 μ , 1.5M ℓ -GV,) , 16,000g 4 15 . , (0.

EMCV()
 : 095001
 : 1997 12
 : [Gresser I. Bourali C, Thomas MT, Falcoff E.
 'Proc Soc Exp Biol Med', 1968 2 , 127:491-6] EM
 CV JH L-929
 : EMCV -70
 -60 EMCV

[I. EEC]		[가]		[(IFFA CREDO) (Institut Federatif) CNRS]	
[가]		[]		[(FCS) [(Eagle's Minimal Essential Medium; MEM) (Finnpipette, Labsystem, 50-300 μ l)]]	
(Gibco)]	80 μ l	(Falcon) ,	: 3072]	5% CO ₂	WISH L929 (2x10 ⁴ / [(Fo
) 2% FCS가	MEM 100 μ l	가 ,	가 ,	37	GLDW (Olympus) IM
rma) 3029 CO ₂]. , 10	가 ,	가 ,	2% FCS가	100 μ l
100 μ l					
, 2% FCS가	MEM 200 μ l		1:10		2
. NIH Mu IFN-	(G-023-901-527)		NIH Mu IFN-	/	(G-002-9004-
5411)	2		2% FCS가	MEM 100 μ l	WISH L
929	(2x10 ⁴ /)		5% CO ₂	37	
			(顯性)		
, VSV 100 TCID ₅₀ (WISH	2x10 ⁻⁴ VSV ₂₃			L929	10 ⁻⁵
VSV ₂₃)	2% FCS가	MEM 200 μ l			
37		IM ULWD			
		가			
		/M ℓ (IU/M ℓ)			
				50%	

1

(EMCV) CNS (Rueckert, R.R., in Virology, Fields ed., 705-738, 1985, ,). IFN-

[(Finter, N.B.)	'Front. of Biol.', 1973 <u>2</u> 135-147	가	EMCV
			EMCV	,
[(JH)	L929	IFN	
			[(Gresser)
'Proc. Soc. Exp. Biol and Med.', 1968 127: 491-496	L929].	(EMC-)	
in/or	200	5×10 ^{8.62} TCID ₅₀	Mu IFN- /	EMCV
N- / 1-8	Mu IFN- /	Hu IFN- 1-8	(1 2), Hu IF	
in/or	IFN	9	6	
가	(200μl)	(1 2)	8	7

[1]

ECMV

IFN	IU/					(%)	(±)
IFN				5	5,5,5,6,6	0	5.4 ± 0.2
MulFN- /	10000	BSA	ip	5	-	100	-
MulFN- /	2000	BSA	ip	5	-	100	-
MulFN- /	200	BSA	ip	5	7,-	80	-
MulFN- /	2000	BSA	in/or	5	7,7,7,8,10	0	7.8 ± 0.6
MulFN- /	200	BSA	in/or	5	7,10,-	60	-
HuIFN 1-8	2000	BSA	ip	5	-	100	-
HuIFN 1-8	200	BSA	ip	5	7,10,-	60	-
HuIFN 1-8	2000	BSA	in/or	5	5,7,11,-	40	-
HuIFN 1-8	200	BSA	in/or	5	5,7,7,-	40	-
0	EMCV			-2, -1, 0, +1, +2	+3		1

[2]

375LD 50 ECMV가

IFN-

			()											
			4	5	6	7	8	9	10	12	13	14	26	
			5/5	5/5	1/5	0/5								
MulFN- /	200IU	in/or	5/5	4/5	4/5	4/5	2/5	2/5	2/5	1/5	1/5	1/5	1/5	1/5
MulFN- /	2000IU	in/or	5/5	5/5	5/5	4/5	3/5	2/5	2/5	2/5	1/5	1/5	1/5	1/5
HuIFN- 1-8	200IU	in/or	4/4	4/4	3/4	3/4	1/4	1/4	1/4	0/4				
HuIFN- 1-8	2000IU	in/or	5/5	3/5	1/5	1/5	0/5							
MulFN- /	200IU	ip	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
MulFN- /	2000IU	ip	5/5	5/5	5/5	5/5	4/5	4/5	4/5	4/5	4/5	4/5	4/5	4/5
MulFN- /	10 ⁻⁴ IU	ip	4/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4
HuIFN- 1-8	200IU	ip	5/5	5/5	5/5	5/5	5/5	4/5	4/5	4/5	4/5	4/5	4/5	4/5
HuIFN- 1-8	2000IU	ip	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
0	EMCV		-2, -1, 0, +1	+2				1	2					

[3]

ECMV

IFN	IU/				%	(±)
		in/or	6	4,4,5,5,6,6	0	5.0 ± 0.4
HuIFN 1-8	2000	ip	5	15,17,-	60	
HuIFN 1-8	200	ip	5	9,10,16,17,17	0	13.8 ± 1.8
HuIFN 1-8	2000	in/or	5	5,6,7,7,21	0	9.2 ± 2.3
HuIFN 1-8	200	in/or	5	5,6,6,7,9	0	6.6 ± 0.7
0	EMCV	0, +1, +2, +3	+4	1	2	.

in/or	ip				1	2		, ip	in/or
	(7/16)			(9/16)		.			
		1	2	IFN	(3)가	1	1	IFN	(1 2)
				가		.		.	

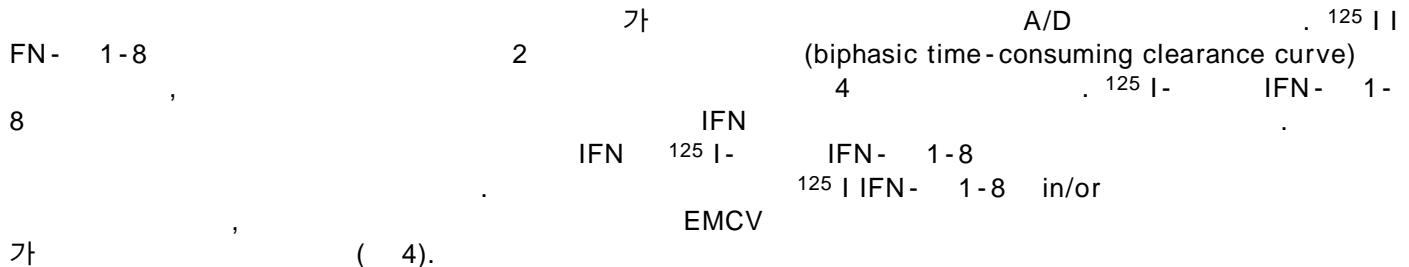
EMCV
 200 2000IU HuIFN- 1-8 in/or ip 가, IFN 가
 4 (3). IFN X 2 (1966)
 EMCV

SV) 100LD50 [10 (Tovey 6 10μℓ 'Proc. Soc. Exp. Biol. Med.', 1974, 146: 406-41
 5]. 7 10μℓ () 10μℓ / 4 1 1
 / VSV 가 .
 , 10,000IU / 30% VSV 21 . 21
 , 가 .

5

IFN 가 IFN-
 70 x 10⁶ IU Hu IFN- 1-8 PBS 1.4M ℓ (Hunter and Greenwo
 od) [Nature, 1962 194:495-496] -T (Mogense
 n) [Int. J. Cancer, 1981 28: 575-582]
 125 I- Hu IFN- 1-8(CGP35269-1) VSV WISH 2 x
 10⁷ IU/M ℓ VSV L929 1 x 10⁶ IU/M ℓ
 6 7 1 x 10⁶ IU 2 x 10⁷ IU 125 I Hu IFN- 1-8(1.0369 x
 10⁷ cpm/) / / , 3 , , ± 1.0 μ g
 , , , , , , (800g x 10⁷, 4) WISH
 L929 , , , , , ,
 SDS-PAGE IFN
 1.0369 x 10⁷ cpm/ 125 I- Hu IFN- 1-8 5 15 30
 (2 x 10⁶ cpm/ml) 1.0369 x 10⁷ cpm 125 I Hu IFN- 1-8 20 5
 30 가 125 I IFN- 1-8 / 5, 10 15
 3가 , 125 I- IFN- 1-8 / M ℓ
 가 IFN
 125 I Hu IFN- 1-8 , 125 I Hu IFN- 1-8 , IFN /
 ,
 IFN
 125 I Hu IFN- 1-8 ,
 SDS- -IFN- , 가 A-G IFN
 125 I Hu IFN- 1-8 (SDS-PAGE) ,
 FN- 1-8 SDS-PAGE , 125 I Hu I
 20000 , 125 I IFN- 1-8 / Hu IFN- 1-8
 , , IFN 125 I IFN- 1-8 4 5
 , , , , , , 15 30
 가 30 125 I IFN- 1-8 15 15 , 30
 , , , , , , 15
 , , , , , , /
 , , , , , ,
 Hu IFN- 1-8

 /
 Hu IFN - 1-8 , 1.0369 x 10⁷ cpm/ 125 I- Hu IFN - 1-8
 , , 24
 125 I- Hu IFN - 1-8 (cl
 earance) A/D(Bgl)[(Bohoslawed
) 'J. IFN Res.', 1986 6: 207-213]



EMCV가 [4] 125I-IFN-

			()											
			3	4	5	6	7	8	9	10	15	30		
			6/6	4/6	2/6	0/6								
Hu IFN 1-8	1.4×10 ⁵ IU	in/or	6/6	5/6	4/6	3/6	1/6	1/6	1/6	1/6	1/6	1/6		
Mu IFN- /	6.4×10 ⁴ IU	in/or	6/6	5/6	5/6	4/6	3/6	2/6	2/6	2/6	1/6	1/6		

IFN
 가 IFN- (Mu IFN- / Mu IFN-) 가 IFN-
 Mu IFN- Mu IFN-
 IFN () , IFN
 (4) , 3가 (MHC IFN- I , Lys6 A/E ,
 2',5'-
 20IU IFN- 3가 IFN-
 가 , 20,000IU IFN- 가
 , IFN , IFN
 , in/or IFN- , IFN-
 가 , in/or IFN- IFN-
 , IFN- , 20,000IU IFN-
 , IFN
 , , IFN
 , Hu IFN- 1-8 , IFN
 , IFN- 1-8 , IFN
 , SDS-PAGE , IFN
 , IFN , , IFN
 , , IFN , , IFN

IFN 가 , IFN , 3가 , IFN 가 .
FN 가 . IFN , FN .
IFN , IFN .

(57)

1. 1500 IU 20 x 10⁶ IU
, 가 , , , , (rhinovirus)

2. 1 5000 IU 20 x 10⁶ IU
3. 2 1 x 10⁴ IU 1 x 10⁶ IU
4. 1 , I:C, (Tilorone) (Imiquimod)
5. 1 , 가
6. 1 , , , , , , (Creutzfeldt-Jakob syndrome),
, , , , , (herpes varicella), B , C , (hum
an immunodeficiency virus: HIV),
(herpes simplex virus: HSV)-1 HSV-2
7. 1 4 , 5 6 ,
8. 1 4 , 5 6 ,
9. 1 4 , 5 6 ,