

(45)
(11)
(24)

2003 12 18
10-0399501
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

[illegible]

(30)	PN 9765	1996 05 09	(AU)
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(73)	-	-	376	6002
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(72)

-75005	7
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(74)

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(54)

· , 가 , ,

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

(Cantell) (Phyhalal) ' J. Gen. Virol.' 1973 20 :97-104; (Wills) 가 [984 4 :399-409; (Gilson) ' J. IFN Res. ', 1985 5 ;403-408 ' J. IFN Res. ', 1 (Plasmodium berghei)].

710; ' *Amer. J. Trop. Med. Hyg.* ', 1969 **18** : 823]. (Sporozoite) (Jahiel) ' *Science* ', 1986 16: 1802; ' *Nature* ', 1968 **220** : (Newcastle)

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

Dis.', 1983 **148** : 914-921]. 가 [(Hayden) ' *J. Infect.* (Douglas) ' *New Engl. J. Med* ', 1986 **314** :65-80; [' *New Engl. J. Med* ', 1986 **314** : 71-75] - 2 가 .

19 (theileriosis) 4,462,985 6085 583332 5,215,741 0.01 5IU

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

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

2. *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium vivax*, *Plasmodium ovale*.

3. HIV, AIDS

가 HIV (protease) 가 IFN (Remington), 'The Science and Practice of Pharmacy', Mack Publishing Co, Easton, PA, 1995 4,496,537

IFN 가

가 (頰側) 가

가, (% /): USP 3%; BP 45%; BP 30%; BP 11%; BP 5%; BPC 4%; BP 2%; 10⁶ IU IFN-2.

(pH 4.5) 25%, 100%가 4,675,184 10⁶ IU IFN- 2 45%, CMC 2%, .

, 가 가

가 가 . ,

00IU 20×10⁻⁶ IU , 가 1500IU, 50
1×10⁻⁴ IU 1×10⁻⁶ IU , 1×10⁻⁴ IU 20×10⁻⁶ IU, 가 .

가

IFN- /
IFN- / (Mu IFN- /) (NDV) C243-3
(' *Proc. Soc. Exp. Biol. and Med.* ', 1974 **146** :809-815
(VSV) 929 4x
10⁶ (IU)/Mℓ 가 1mg 5x10⁷ IU 가 (' *Proc. Soc. Exp. Biol. and Med.* ', 1974 **146** :809-815). (NIH) IFN- / (G-002-9004-5411)
IFN- 1-8
IFN- 1-8 [Hu IFN- 1-8; BDBB : CGP 35269-1, 가 (Ciba-Geigy)] (Meister) ' *J. Gen. Virol.* ', 1986 **67** :1633-1643].
(' *Nature* ', 1977 267:455-457) VSV WISH 70x10⁶ IU/Mℓ 가 가 L929
1x10⁶ IU/Mℓ 가 가 NIH IFN- (G-023-901-527) NIH IFN-
- / (G-002-9004-5411) . IFN 1mg 2x10⁸ IU .
-
(Life Technologies Inc.)
Mℓ 가 (: HKK 404) VSV L929 6x10⁶ IU/
1mg 6x10⁸ IU 가 (' *Proc. Soc. Exp. Biol. Med.* ', 1974, 146:406-415).
-
(Ramp;D Systems Inc.)
Mℓ 가 (: 1976-01S) VSV L929 3.2x10⁴ IU/
1mg 8x10⁶ IU 가 (' *Proc. Soc. Exp. Biol. Med.* ', 1974, 146:406-415).
-
(: 2580-03SA) VSV L929 2x10⁵ IU/Mℓ 가 (1
mg 1x10⁷ IU 가 (' *Proc. Soc. Exp. Biol. Med.* ', 1974, 146:406-415).
(G-002-9004-5411) 가 , /
(Ferimmune,)
-
(BSA) V[R
IA ; ; A7888; (Sigma)] PBS(pH 7.4) 1Mℓ 100μg
[0.2 μ, (Millex)-GV, (Millipore)].

[, (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

40 BP) 0.03% : () BP () 44.64% BP(

2 μ , 1.5M ℓ -GV,) , 16,000g 15 , (0.

_____, P20 5 $\mu\ell$ (外鼻孔) 가 30 125 | - IFN- 1-8 , IFN 'in/or' IFN 가 IFN

EMCV() : 095001 : 1997 12 : [Gresser I. Bourali C, Thomas MT, FalcoffE. 'Proc Soc Exp Biol Med', 1968 2 , 127:491-6] EM CV JH L-929 L929 5 $\times 10^{8.62}$ TCID₅₀ 가 가 : EMCV -70 가 1 가 8 , -70 -60 EMCV

_____, 가 [(IFFA CREDO) (Institut Federatif) CNRS]. 가 EEC

_____, (20 $\mu\ell$) 2% - (FCS)[(Gibco)] (Eagle's Minimal Essential Medium; MEM)() 80 $\mu\ell$, (Finnpipette, Labssystem, 50-300 $\mu\ell$) [(Falcon) , : 3072] 가 . WISH L929 (2 $\times 10^{-4}$ /) 2% FCS가 MEM 100 $\mu\ell$ 가 , 5% CO₂ 37 [(Fo rma) 3029 CO₂]. , 10 가 (Olympus) IM GLDW , 2% FCS가 100 $\mu\ell$, 2% FCS가 MEM 200 $\mu\ell$ 1:10 2 (G-023-901-527) NIH Mu IFN- / (G-002-9004- 5411) 2 2% FCS가 MEM 100 $\mu\ell$ WISH L 929 (2 $\times 10^{-4}$ /) 가 , 5% CO₂ 37 (顯性) 2 $\times 10^{-4}$ VSV₂₃ , L929 10⁻⁵ VSV₂₃) 2% FCS가 MEM 200 $\mu\ell$ 50% IM ULWD 가 50% /M ℓ (IU/M ℓ)

_____, 1

(EMCV)

CNS

(Rueckart, R.R., in Virology, Fields ed., 705-738, 1985,

,). IFN-

가
[(Finter, N.B.) 'Front. of Biol.', 1973 2 135-147
]. , EMCV
(JH) L929 IFN
'Proc. Soc. Exp. Biol and Med.', 1968 127: 491-496 [(Gresser)
L929 $5 \times 10^{8.62}$ TCID₅₀ 가 가 . (EMC-)
in/or 200 2000IU Mu IFN- / Hu IFN- 1-8 EMCV
가 (300LD₅₀). 6 (1 2) , Hu IF
N- / 1-8 Mu IFN- /
in/or IFN 9 6
가 .
(200 μ l) (1 2) 8 7
가 .

[1]

ECMV

IFN	IU/					(%)	(\pm)
IFN				5	5,5,5,6,6	0	5.4 \pm 0.2
MuIFN- /	10000	BSA	ip	5	-	100	-
MuIFN- /	2000	BSA	ip	5	-	100	-
MuIFN- /	200	BSA	ip	5	7,-	80	-
MuIFN- /	2000	BSA	in/or	5	7,7,7,8,10	0	7.8 \pm 0.6
MuIFN- /	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	ECMV	-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							
MuIFN- /	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
MuIFN- /	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
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						
MuIFN- /	200IU	ip	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5	5/5
MuIFN- /	2000IU	ip	5/5	5/5	5/5	5/5	4/5	4/5	4/5	4/5	4/5	4/5	4/5
MuIFN- /	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
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
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
0	ECMV	-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 (7/16) 1 2 , ip in/or
(9/16)
(3)가 1 1 IFN (1 2)
가

2
EMCV

200 2000IU HuIFN- 1-8 in/or ip IFN 가 EMCV
4 가, IFN 가 4

(3).

IFN

X 2

(1966)
가

EMCV

3

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

4

IFN-
IFN
3 IFN- MHC I , Ly 6A/E 2'-5'-
, IFN- IFN- 가
20IU Mu IFN- 가 H-2-K^d
가 , / 20,000IU Mu IFN- DBA-2 (H-2K^d)
^d) , / 20,000IU IFN- Ly6 A/E
(Dumont) 'J. Immunol', 1986 137:201-210]. / 200 20,000IU Mu
IFN- 20IU Hu IFN- (Swiss) DBA/2
Mu IFN- 2',5'- 가
/ 20,000IU Mu IFN- , / 200 20,000IU 2',5'-
8 IFN 10 20,000IU Mu IFN- Hu IFN- 1-
2',5'-

[illegible]

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

가 A/D 125 I I
 FN- 1-8 2 (biphasic time-consuming clearance curve)
 8 , 4 125 I- IFN- 1-
 IFN 125 I- IFN- 1-8
 IFN 125 I IFN- 1-8 in/or
 EMCV
 가 (4).

[4]

EMCV가

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

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

(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)

가

5. 1 , 가

6. 1 , , , , , (Creutzfeldt-Jakob syndrome),
(herpes varicella), B , C (hum
an immunodeficiency virus: HIV),
(herpes simplex virus: HSV)-1 HSV-2 (human papilloma virus: HPV),

7. 1 4 , 5 6 ,

8. 1 4 , 5 6 ,

9. 1 4 , 5 6 ,