

C57BL/6

(B-16)

Holmium-166

C57BL/6

(B-16)

Holmium-166

2000

12

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가

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	.....	1
I.	.....	3
II.	.....	4
1.	.....	4
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1.		.....	6
2.	Ho-166	.....	8
3.	Ho-166	.....	8
4.	Ho-166	(in log scale) .....	8
5.	Ho-166 (survival rate)	.....	9

C57BL/6

(B-16)

Holmium-166

가  
가

가 , 가  
가  
가

가 Ho-166 가

C57BL/6 , Holmium-166 가  
(B-16) Ho-166  
(growth delay effect),  
C57BL/6 (B-16)  $5 \times 10^5$  C57BL/6  
9 10 1 cm  
4 1 mCi (0.3 ml volume), 5 mCi (0.3 ml volume), 5 mCi (0.5  
ml volume) Ho-166  
0.3 ml volume

Ho-166  
. Ho-166 2 (length)  
, Ho-166  
(tumor growth delay) . Ho-166  
C57BL/6  
Ho-166 C57BL/6 1, 2, 3, 7, 14, 17

2

Ho-166 1  
, Ho-166

C57BL/6 가 3  
가 . H-E , Ho-166  
가  
3  
. Ho-166



0.3 ml  
가 . 5 mCi 0.5 ml 5 mCi  
Ho-166  
, Ho-166

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: , Holmium-166, (internal radiation therapy),  
C57BL/6 , B-16

C57BL/6

(B-16)

Holmium-166

< >

I.

가 가 ,  
 가 가 ,  
 가 가 Deacon  
 Bjork-Ericksson  
 (radiocurability) 가 E ,  
 가 surviving fraction (SF) value  
 가  
 가 가  
 가  
 (internal radiation therapy) ,  
 2.5 mm, 10.3 mm  
 ,  
 Phosphorus-32 (P-32), Yttrium-90 (Y-90), Rhenium-186  
 (Re-186), Rhenium-188 (Re-188), Holmium-166 (Ho-166)

Holmium-166 Holmium-165 26.83 94%  
 [ 0.61 MeV, 1.766 MeV (48%), 1.855 MeV (51%)] 6% [0.081  
 MeV (6.24%), 1.379 MeV (0.93%)] Y-90 ( 0.93 MeV, 2 MeV)

<sup>14</sup> Ho-166 (penetration range)  
 1.23 mm, 8.6 mm 90% 가 2.1 mm  
 , 10% 2.1 8.6 mm

<sup>16</sup> Brown Ho-166  
 Ho-166 DNA ,  
 Ho-166 <sup>19</sup>  
 (SK-HEP1) Ho-166

<sup>20</sup>  
 Ho-166 가 가 ,  
 Ho-166 skin patch  
 , 가 <sup>21,22</sup>  
 Ho-166  
 Ho-166 ,

Holmium-166 가  
 Ho-166 가 가

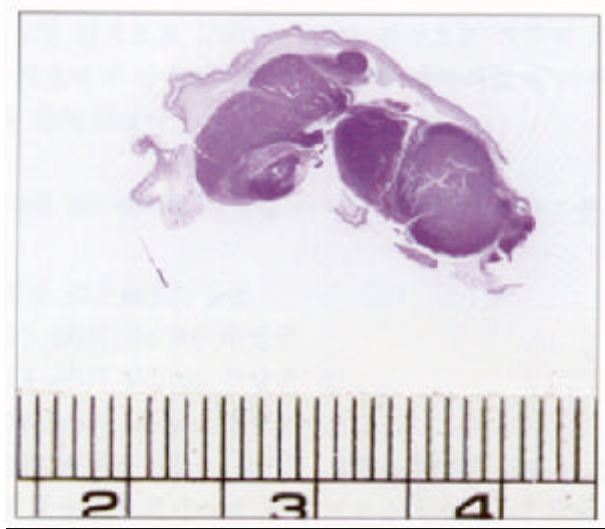
## II.

### 1.

#### 가. Ho-166

<sup>165</sup>-Ho(NO<sub>3</sub>)<sub>3</sub>·5H<sub>2</sub>O NaOH NaBH<sub>4</sub> Ho-165  
 (macroaggregates) , 1 × 10<sup>3</sup> n/cm<sup>2</sup> sec neutron flux  
<sup>166</sup>-Ho(NO<sub>3</sub>)<sub>3</sub>

C57BL/6



1. C57BL/6

B-16  $5 \times 10^5$

C57BL/6

10

22

55%

SPF (specific pathogen free)

(RO water)

(PMI)

C57BL/6

B-16

RPMI 1640 (Gibco laboratories, Grand Island, NY,

USA)  $56^\circ\text{C}$

30

(Gibco), 2 mM L-glutamine (Gibco), 100

IU/ml penicilline

100 ug/ml streptomycin (Gibco)

가

$5 \times 10^5$ ,  $1 \times 10^6$

C57BL/6

$1 \times 10^5$ ,

14

9

$10^5$

가 가

$5 \times 10^5$

( 1).

2.

가.

C57BL/6

B-16  $5 \times 10^5$

C57BL/6

9 10

2 1/100 mm 가 digimatic caliper  
 (Mitutoyo, Japan) , 1 cm  
 Ho-166 .

Mouse melanoma cell line (B-16) C57BL/6 4

- 1 : (0.3 ml)
- 2 : 1 mCi (0.3 ml) Ho-166
- 3 : 5 mCi (0.3 ml) Ho-166
- 4 : 5 mCi (0.5 ml) Ho-166

140 C57BL/6 1, 2, 3, 4

1, 2, 3, 7, 14, 17 2 , 1 25 , 2  
 15 , 3 27 , 4 25 1 ( ) C57BL/6 가  
 ( 1).

**Ho-166**

C57BL/6 (dose calibrator)

Monte Carlo simulation Ho-166 1 mCi (0.3 ml volume),  
 5 mCi (0.3 ml volume), 5 mCi (0.5 ml volume)  
 , 0.3 ml volume

1 mCi (0.3 ml), 5 mCi (0.3 ml), 5 mCi (0.5 ml) Ho-166 C57BL/6

1, 2, 3, 7, 14, 17 (Vertex, ADAC,

Milipitas, USA) C57BL/6 5 cm

**1.**

( )			
1	37	12	25
2	27	12	15
3	39	12	27
4	37	12	25
140		48	92

Ho-166 2 1/100 mm 가  
 digimatic caliper  
 (length, A) (width, B)  
 Ho-166  
 (A) (B)  
 $= 1/2 \times A^2 \times B$

ANOVA test  
 (Survival rate)  
 Ho-166 C57BL/6 가 3 (B-16  
 29 , Ho-166 20 ) Ho-166 C57BL/6  
 (survival curve)

logrank test  
 Ho-166 1, 2, 3, 7, 14, 17 2 가  
 , Ho-166  
 hematoxylin-eosin

### III.

1.  
 Ho-166 ( 2) ( 3 &  
 4, 2) (p < 0.001)  
 , Ho-166  
 2  
 . Ho-166 4  
 Ho-166

**2. Ho-166**

	9	11	13	17	19	21	24	26	28
	10.4	15.3	17.6	20.9	23.8	28.1	34.3	38.5	39.0
1 mCi (0.3 ml)	10.0	12.6	12.5	11.9	11.4	11.8	11.3	9.1	8.0
5 mCi (0.3 ml)	10.4	12.9	12.4	11.9	11.7	11.4	11.2	10.0	8.2
5 mCi (0.5 ml)	10.1	11.9	11.8	11.5	11.3	11.1	10.7	8.3	8.1

Unit of tumor length: mm

**3. Ho-166**

	9	11	13	17	19	21	24	26	28
	631.9	1514.4	3730.2	6371.3	10106.6	15092.1	17304.2	19976.6	24251.8
1 mCi (0.3 ml)	513.2	896.3	869.5	810.6	798.6	816.8	738.5	311.8	279.3
5 mCi (0.3 ml)	626.8	916.5	899.8	819.2	836.2	799.6	704.2	559.9	242.5
5 mCi (0.5 ml)	492.5	820.0	826.7	663.0	703.7	640.7	497.3	208.1	243.9

Unit of tumor volume: mm<sup>3</sup>

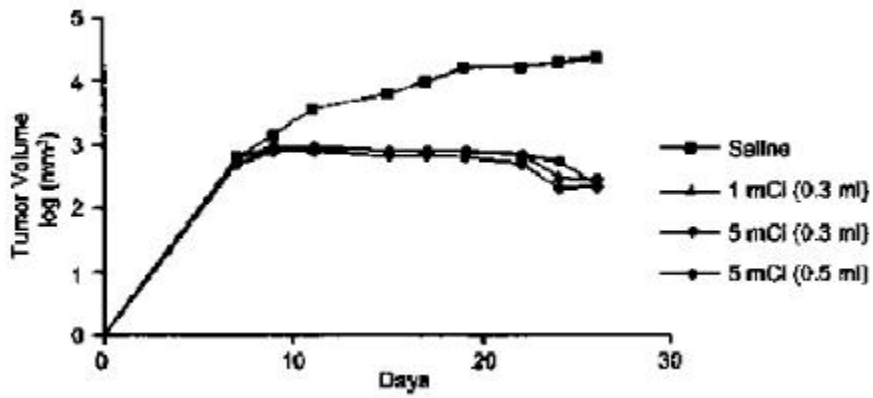
**4. Ho-166 (in log scale)**

	9	11	13	17	19	21	24	26	28
	2.80	3.18	3.57	3.81	4.00	4.22	4.24	4.30	4.39
1 mCi (0.3 ml)	2.70	2.95	2.99	2.91	2.90	2.91	2.87	2.49	2.45
5 mCi (0.3 ml)	2.80	2.99	2.96	2.91	2.92	2.90	2.85	2.75	2.38
5 mCi (0.5 ml)	2.69	2.91	2.91	2.82	2.84	2.81	2.70	2.32	2.35

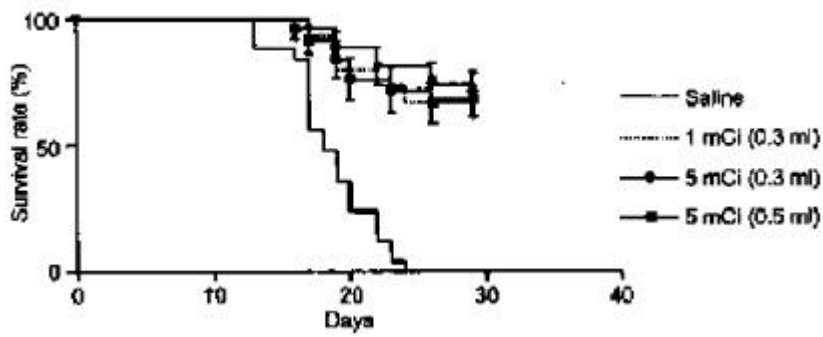
Unit of tumor volume: log (mm<sup>3</sup>)

**2. Ho-166**

benefit (5, 3). Ho-166 (p < 0.0001) survival  
 volume) 가 . 3 (5 mCi, 0.3 ml)



2. Ho-166 (in log scale)



3. Ho-166

5. Ho-166 (survival rate)

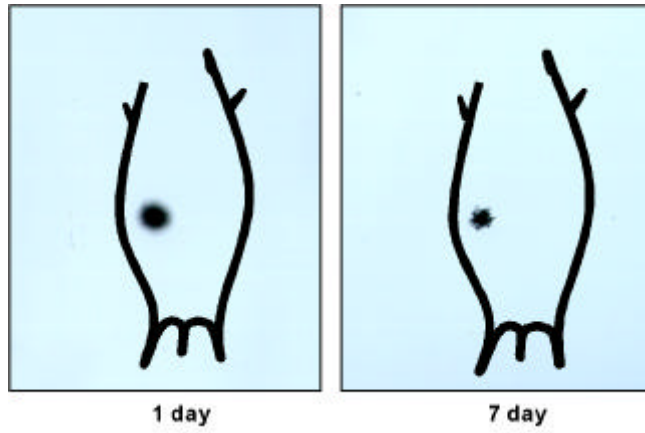
	9	13	16	17	18	19	20	22	23	24	26	29
Control	100	88.0	84.0	56.0	48.0	36.0	24.0	12.0	4.0	4.0	0	0
1 mCi	100	100	100	93.3	93.3	80.0	80.0	73.3	73.3	66.7	66.7	60.0
5 mCi (0.3 ml)	100	100	100	96.3	96.3	88.9	88.9	81.5	81.5	81.5	74.1	70.4
5 mCi (0.5 ml)	100	100	96.0	92.0	92.0	84.0	76.0	76.0	72.0	72.0	68.0	68.0

: %

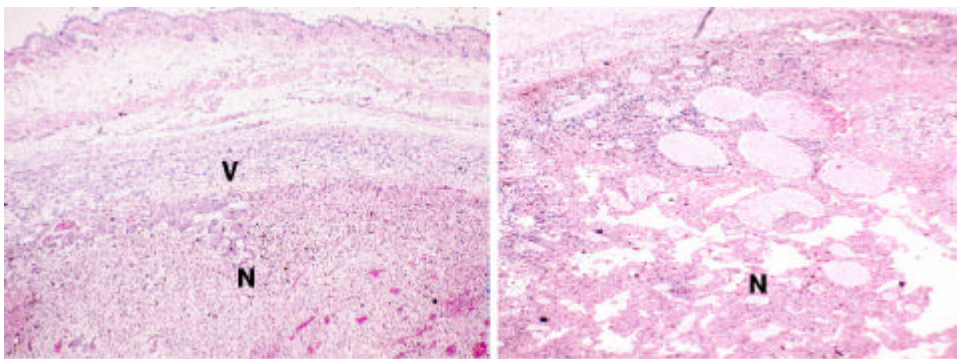


3.

166 Ho-166 Ho-166  
 , Ho-166 ( 4).



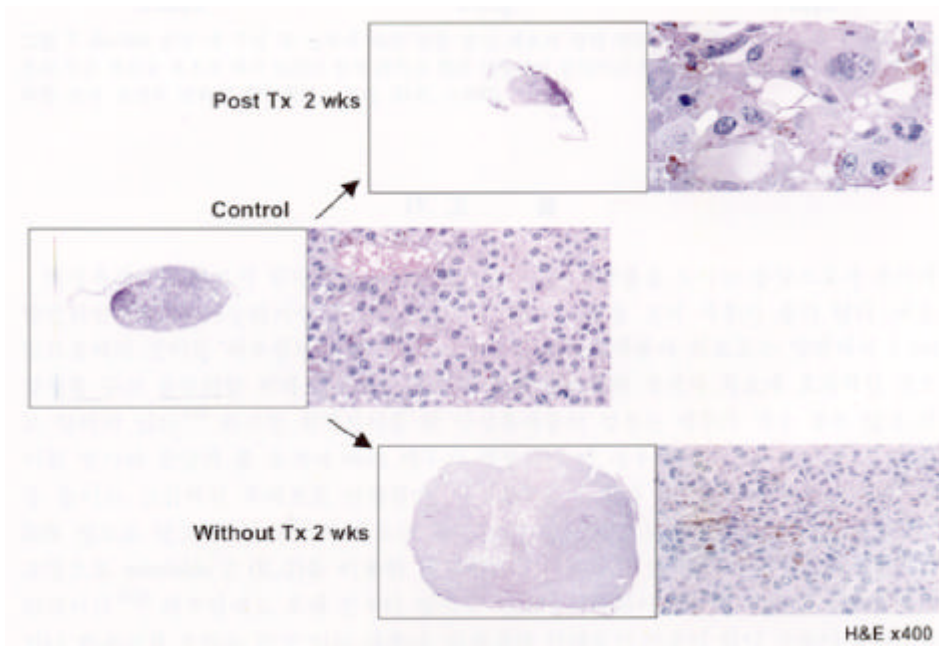
4. Ho-166 1 7 . 1  
 Ho-166 , 7



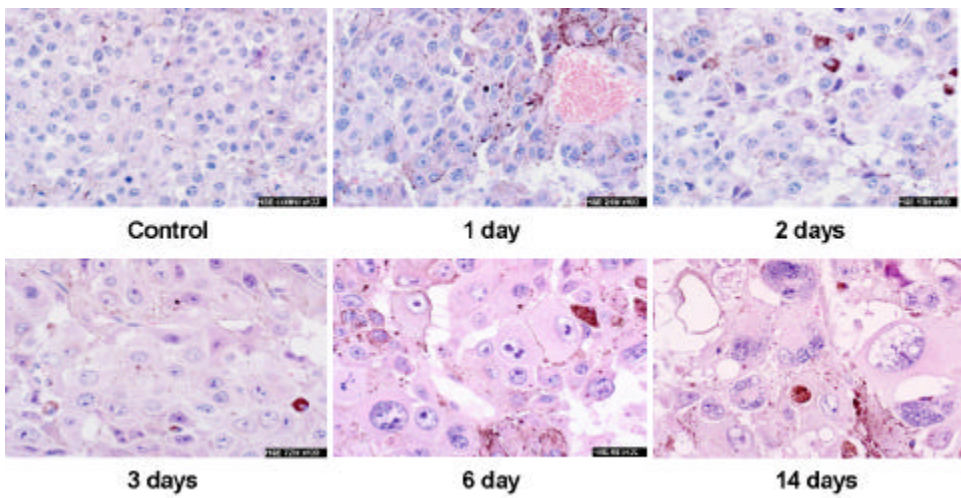
5. Ho-166 . Ho-166 1 ( ) 2 ( )  
 (H-E, ×40). (N) (V)가

4. Ho-166

가 , Ho-166 1  
 가 ( 5). Ho-166 3  
 가  
 ( 6, 7). 4  
 가 .



6. Ho-166 2 ( ) ( ) H&E  
 Ho-166 2 가 가  
 가 , Ho-166 가 가 가  
 가



7. Ho-166

가 가 (H-E,  $\times 400$ ).

#### IV.

가 가 가 가 .  
 가 2 cm 가 1 cm  
 가 가

4,23

가

20%

interlukin 2 (IL-2)

24,25

가

가

26

가 가

가

가

4,5

1936

Paterson

sensitive, intermediate

radioresistant 3가 , radioresistant 가  
.<sup>26</sup> Ionizing radiation

가 .<sup>7</sup>

가

2 Gy (surviving fraction at 2 Gy, SF<sub>2</sub>), mean activation  
dose (D) alpha .<sup>27</sup> Deacon<sup>6</sup> 가 A ( , ) 가  
radiocurability E 가 E

E

가

.<sup>28,29</sup>

SF<sub>2</sub>가 가

가

.

가

.<sup>28</sup>

Bjork-Ericksson

clonogenic assay

.<sup>7</sup>

surviving fraction (SF)

value

.<sup>8,9,30-32</sup>

Ho-166

survival benefit

.

Ho-166

가

,

, 가

가

2.5 mm, 10.3 mm

Iodine-131 (I-131), Phosphorus-32 (P-32), Yttrium-90 (Y-90), Rhenium-186 (Re-186), Rhenium-188 (Re-188), Holmium-166 (Ho-166)  
가 Y-90, Re-186, Ho-166 가

Ho-166 26.83 가 64 Y-90  
가 , 94% [ 0.61 MeV, 1.766 MeV (48%), 1.855 MeV (51%)]  
6% [0.081 MeV (6.24%), 1.379 MeV (0.93%)] Y-90

가 ,  
<sup>14</sup> Ho-166 1.23 mm, 8.6 mm  
90% 가 2.1 mm , 10%

2.1 8.6 mm

(SK-HEP1) Ho-166

가 <sup>20</sup> Ho-166  
Ho-166 가 가  
(skin patch)

<sup>21,22</sup>

Ho-166

Ho-166

HEP1) Ho-166-chitosan

(SK-0.025

ml , 1 cm

3.7 mCi , 2 cm

10.94 mCi

0.5 mCi

252 Gy

1.0 mCi

504 Gy

가

가 <sup>16</sup>

1 cm

Monte Carlo simulation

5 mCi

1 cm

가

5 mCi

1 mCi

. 1 mCi

가 , Ho-166 ,  
0.3 0.5 ml 가 , 1 mCi 가  
pressure) , (interstitial 가  
가 1 cm Ho-166  
가 가 Ho-166  
가  
<sup>32</sup>  
(SK-HEP 1) Ho-166-chitosan  
<sup>33</sup>  
Ho-166 chitosan 가 Ho-166  
Ho-166-chitosan 가 Ho-166  
Ho-166  
<sup>34</sup>  
4 5 3 1  
Ho-166  
Ho-166  
가  
Ho-166

, Ho-166  
가

V.

가 가  
Ho-166 가 가  
, C57BL/6 B-16 C57BL/6  
9 10 ,  
Ho-166 ,

1. Ho-166 , Ho-166 , 가

2. Ho-166 1

가 Ho-166 가  
5 mCi (0.5 ml volume)

3. 가 3  
Ho-166 가  
Ho-166 가 5 mCi  
(0.3 ml volume) 가

5. , Ho-166 가  
,  
Ho-166 1  
가 , 가

6. 5 mCi (0.5 ml volume)	5 mCi (0.3 ml volume)	1 cm	가
	1 mCi (0.3 ml volume)		
Ho-166			
	Ho-166		

, Ho-166

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## Abstract

### **Effect of Holmium-166 injection into malignant melanomas (B-16) transplanted in C57BL/6 mice**

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(Directed by Professor Jong Doo Lee)

Malignant melanoma is an uncommon human cancer with a high mortality rate. Surgical treatment at the early stages of melanoma is usually curative. Radiotherapy is indicated when plastic repair is difficult or when the patient is a poor candidate for surgery. External beam radiotherapy can be used in the management of unresectable malignant melanoma; however, normal soft tissue tolerance prevents the administration of tumoricidal doses. In comparison, internal radiation therapy of a tumor by percutaneous injection of beta-emitting radionuclide can give high radiation doses to the specific tumor to kill tumor tissue without any radiation damage to the normal neighboring tissues. Therefore, beta emitters, which have physical characteristics of high linear energy transfer and rapid fall off and limited penetration ranges (several mm), can be reliably applied to internal radiation therapy. Ho-166 is a potent beta emitter which has a short half-life (26.8 hours) and high beta energy, and a small amount of gamma emission (5%) can be used as radiation activity tracer. However, radiore-sponsiveness and radiocurability of the malignant melanoma have been known to be very low. This study was to evaluate the feasibility and effectiveness of Ho-166 injection into malignant melanoma transplanted in C57/BL6 mice.

We transplanted mouse melanoma cell line (B-16) into C57BL/6 mice. After getting tumor masses of 1 cm in longitudinal dimension, we injected variable doses and volumes of Ho-166 into the tumor via a percutaneous route in 140 C57BL/6 mice including normal control [Group I (n=37)] which got no radiotherapy. Group II (n=27) received dose of 1 mCi (0.3 ml volume) and Group III (n=39) received dose of 5 mCi (0.3 ml volume) and group IV (n=37) received dose of 5 mCi (0.5 ml volume). We evaluated the growth delay and survival rate after Ho-166 injection by serial assessment of the size of the tumor and survival proportion. Whole body static gamma camera images were obtained serially to evaluate tumor uptake. We sacrificed C57BL/6 mice in 1, 2, 3, 7, 14, 17 days and performed histopathologic examinations.

Whole body scintigraphy using gamma camera revealed accumulation of radiotracer activity within the tumor without any radioactivity in other organs. When compared to control groups, evident growth delay and survival benefit were noted on Ho-166 treated groups irrespective of the radiation dosage and injection volume. Microscopically, marked coagulation necrosis in the center of the tumor was noted in groups with Ho-166 injection. And cytologic features of radiation-induced cellular damages were prominent in the peripherally located tumor cells from 3 days after Ho-166 injection. Skin necrosis and ulcer were seen in some mice of group IV and in group III.

In conclusion, the radiation effect of Ho-166 was highly appreciated in malignant melanomas by giving enough radiation to kill tumor tissues without any radiation damage on the neighboring tissues. The clinical application of Ho-166, particularly by intratumoral injection is thought to be promising as a new and minimally invasive treatment modality of malignant melanomas that have been known as radioresistant.

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Key Words: Malignant melanoma, Holmium-166, internal radiation therapy, C57BL/6 mouse, B-16