Trial decision

Invalidation No. 2012-800093

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The case of trial regarding the invalidation of Japanese Patent No. 2664261, titled "ANIMAL MODEL FOR HUMAN DISEASE" between the parties above has resulted in the following trial decision:

Conclusion

The trial of the case was groundless.

The costs in connection with the trial shall be borne by the demandant.

Reason

No. 1 History of procedures

This application is an application with an international application date of October 5, 1989 (claiming priority with a Foreign Patent Office receipt date of October 5, 1988, United States under the Paris Convention for the Protection of Industrial

Property) in connection with the inventions according to Claims 1 to 19 of the Patent No. 2664261. The history of procedure in the Invalidation Trial of the case is as follows.

In addition, the respective items of Evidence A and Evidence B are hereinafter collectively represented as like A1, etc. with A or B and the number of each evidence.

June 20, 1997 Establishment of the patent right
April 15, 1998 Written opposition to the grant of a patent
March 30, 1999 Written correction request
On May 14, 1999 Decision to accept the Correction and maintain the Patent
June 1, 2012 Written Demand for Invalidation (from the demandant) (Evidence A No. 1 to A No. 8)
On September 20, 2012 Written reply (from the demandee) (Posted on September 21, 2012) (Evidence B No. 1 to B No. 24)
On September 20, 2012 (Posted on September 21, 2012) Written correction request (from the demandee)
October 2, 2012 Written Amendment (from the demandee)
October 2, 2012 Written statement (from the demandee)
On November 29, 2012 Decision of dismissal of procedure with respect to the procedure according to the written correction request on September 21, 2012 (the Body)
On January 29, 2013 Written statement (from the demandant) (Posted on January 30, 2013)
On February 13, 2013 Notification of Matters to be examined (the Body)
February 26, 2013 Written Amendment (from the demandee)
February 26, 2013 Written statement (from the demandee) (Evidence B No. 6)
April 4, 2013 Oral proceedings statement brief (from the demandant) (Evidence A No. 9 to A No. 14)
April 4, 2013 Written statement (from the demandee)
April 4, 2013 Oral proceedings statement brief (from the demandee) (Evidence B No. 25 to B No. 51)
April 16, 2013 Written statement (from the demandee) (Evidence B No. 39-2)
April 18, 2013 First Oral proceeding
April 24, 2013 Written statement (from the demandee)
April 24, 2013 Written statement (from the demandee) (Evidence B No. 52)
June 7, 2013 Written Statement (from the demandant) (Evidence A No. 15 to A No. 18)
June 7, 2013 Written statement (from the demandee) (Evidence B No. 53 to B No. 67)
July 30, 2013 Written statement (from the demandee)
August 5, 2013 Written Statement (from the demandant)
August 19, 2013 Written statement (from the demandee) (Evidence B No. 68-1 to B No. 73-2)
August 27, 2013 Written Statement (from the demandant)

No. 2 Demandant's allegation
1 Summary of reasons for invalidation

Demandant seeks for a trial decision to the effect that the patents granted for the Inventions recited in Claims 1 to 19 of the scope of the claims of Patent No. 2664261

should be invalidated, and the costs in connection with the trial shall be borne by the demandee, and submits means of proof as shown in the following "2 Means of Proof" in the written demand for trial and the oral proceeding (including oral proceedings statement brief and record), and presents the following allegation of reasons for invalidation: The allegation of the reasons for invalidation thus far may be summarized as set forth below.

(1) Reasons for invalidation 1 [Violation of Article 29(1), main paragraph of the Patent Act (Incomplete Invention)]

Inventions 1 to 19 are not configured specifically and objectively to the extent that the technical content can bring about a targeted technical effect through the repetitive implementation by a person skilled in the art, and thus these inventions are incomplete inventions, and do not comply with the requirement as provided in Article 29(1), main paragraph of the Patent Act. Therefore, the patents with respect to Inventions 1 to 19 correspond to Article 123(1) of the Patent Act, and thus should be invalidated. (Written Demand, page 11, lines 11 to 20)

(2) Reasons for Invalidation 2 [Violation of Article 36(3) of the Patent Act (Violation of enablement requirement)]

The specification fails to confirm the occurrence or non-occurrence of metastasis of tumor, which is a purpose and an effect of the Invention, and fails to describe what constitution can achieve the purpose of the Invention and bring the effects of the Invention. Specifically, it cannot be said that the Detailed Description of the Invention of the specification describes the purpose, the constitution and the effects of the invention to the extent that allows a person who had ordinary knowledge in the art to which the invention belong to easily implement the invention. Thus the invention does not conform to the requirement as provided in Article 36(3) of the Patent Act. Therefore, the patents with respect to Inventions 1 to 19 correspond to Article 123(1) of the Patent Act, and thus should be invalidated. (Written Demand, page 11, line 21 to page 12, line 8)

(3) Reasons for Invalidation 3 [Article 36(4)(i) of the Patent Act (Violation of supporting requirement)]

The specification fails to confirm the occurrence or non-occurrence of metastasis of tumor, which is a purpose and an effect of the Invention, and fails to describe what constitution can achieve the purpose of the Invention and bring the effects of the Invention. Specifically, the specification is totally silent about the description supporting the function and effect of "an implanted neoplastic tissue metastasizing." Thus it fails to describe or suggest to the extent that allows a person skilled in the art to recognize that the problem to be solved by the Invention would be solved, nor could it be recognized by a person skilled in the art from the common general knowledge as of the filing that the problem would be solved. Therefore, the recitation of the claims goes beyond the scope of the technical matter described and disclosed in the Detailed Description of the Invention of the specification, and thus the Detailed Description of the Invention does not conform to the requirement as provided in Article 36(4)(i) of the Patent Act. Therefore, the patents with respect to Inventions 1 to 19 correspond to Article 123(1) of the Patent Act, and thus should be invalidated. (Written Demand, page

12, lines 9 to 21)

(4) Reasons for Invalidation 4 [Violation of Article 36(4)(ii) of the Patent Act (Violation of description requirement with regard to constituent elemental function of claim)]

The specification fails to describe a method for solving a technical problem on "metastasis"; i.e., the technical matter essential for inducing metastasis, and it is highly likely that the examples of the specification comprising all the constituent elements of the Invention did not induce the metastasis of tumor, which was a purpose and an effect of the Invention. Therefore, it is recognized that the recitation of the scope of claims of the specification on the premise that a non-human animal model of the Invention has an ability to metastasize does not recite all the indispensable constituent features of the invention for which a patent is sought. Thus the scope of claims does not conform to the requirement as provided in Article 36(4)(ii) of the Patent Act. Therefore, the patents with respect to Inventions 1 to 19 correspond to Article 123(1) of the Patent Act, and thus should be invalidated. (Written Demand, page 12, line 22 to page 13, line 7)

(5) Reasons for invalidation 5 [Violation of Article 29(1)(iii) of the Patent Act (Novelty) or Violation of Article 29(2) of the Patent Act (Inventive step)]

All of Inventions 1 to 19 correspond to the inventions of Article 29(1)(iii) of the Patent Act, or violate Article 29(2) of the Patent Act, which are the two reasons for invalidation as set forth below. Therefore, these Inventions correspond to Article 123(1) of the Patent Act, and thus should be invalidated. (Written Demand, page 13, lines 8 to 13)

(5-1) Reasons for invalidation 5-1

Inventions 1 to 3, 10 to 13 are the invention described in A1, or were at least easily conceivable by a person skilled in the art on the basis of the invention described in A1, and Inventions 4 to 9, 14 to 19 were easily conceivable by a person skilled in the art on the basis of the invention described in A1 and the common technical knowledge. (Written Demand, page 13, last line to page 14, line 3)

(5-2) Reasons for invalidation 5-2

Inventions 1 to 3, 6, 11 to 13, 16 are the invention described in A2, or were at least easily conceivable by a person skilled in the art on the basis of the invention described in A2, and Inventions 4 to 5, 7 to 10, 14 to 15, and 17 to 19 were easily conceivable by a person skilled in the art on the basis of the invention described in A2 and the common technical knowledge. (Written Demand, page 14, lines 5 to 8)

(5-3) Reasons for invalidation 5-3

Inventions 1 to 19 were easily conceivable by a person skilled in the art on the basis of the invention described in A3 and each technique described in A1 and A2 (and common technical knowledge). (Written Demand, page 14, lines 11 to 13)

(5-4) Reasons for invalidation 5-4

Inventions 1 to 19 were easily conceivable by a person skilled in the art on the basis of the invention described in A4 and each technique described in A1 and A2 (and

common technical knowledge). (Written Demand, page 14, lines 15 to 17)

If "neoplastic tissue obtained from a human organ" of Claim 1 is construed as including one that has undergone subcutaneous passage, the following reasons for Invalidation (5-5) and (5-6) are added. (Written demand, page 14, line 3 from the bottom to page 15, line 2)

(5-5) Reasons for invalidation 5-5

Inventions 1 to 3, 11 to 13 are the invention described in A3, or were at least easily conceivable by a person skilled in the art on the basis of the invention described in A3, and Inventions 4 to 10, 14 to 19 were easily conceivable by a person skilled in the art on the basis of the invention described in A3 and the common technical knowledge. (Written Demand, page 15, lines 5 to 9)

(5-6) Reasons for invalidation 5-6

Inventions 1 to 3, 11 to 13 are the invention described in A4, or were at least easily conceivable by a person skilled in the art on the basis of the invention described in A4, and Inventions 4 to 10, 14 to 19 were easily conceivable by a person skilled in the art on the basis of the invention described in A4 and the common technical knowledge. (Written Demand, page 15, lines 10 to 14)

(5-7) Reasons for invalidation 5-7

There are the same reasons for invalidation as the above Reasons for invalidation 5-1 and Reason for Invalidation 5-2. (Written Demand, page 15, line 15 to page 16, line 2)

2 Means of Proof

Evidence A No. 1: Journal of the National Cancer Institute, vol. 55, no. 6, December 1975, pp. 1461-1466, and the translation thereof

Evidence A No. 2: Article of the 35th Annual Meeting of the Japanese Cancer Association, October 1976, page 171, Subject 624

Evidence A No. 3: Journal of Clinical and Experimental Medicine, Vol. 104, January 7, 1978, pages 31 to 33

Evidence A No. 4: Kanzo, Vol. 21, No. 3, March 25, 1980, pages 303 to 315

Evidence A No. 5: English-Japanese Dictionary, Kenkyusha, 4th Edition, 1977, page 66

Evidence A No. 6: Tokyo District Court The case of 1999 (Wa) 15238 (Judgment on December 20, 2001)

Evidence A No. 7: Tokyo District Court The case of 2002 (Ne) 675 (Judgment on October 10, 2002)

Evidence A No. 8: Tokyo District Court, The case of 2009 (Wa) 31535 (Judgment on April 27, 2012)

Evidence A No. 9: Excerpt of law available from e-Gov (http://www.e-gov.go.jp/)

Evidence A No. 10: A website of Legislative Bureau House of Councillors, Columns of legislative work, "Transitional provision and the effect of old law - 'the provisions then in force remain applicable' and 'the provisions remain in force' -"
A print out of http://houseikyoku.sangiin.go.jp/coluinn/coluran051.htm

Evidence A No. 11: CANCER RESEARCH, vol. 38, 1978, pp. 2651 to 2652, 1978, and

the translation thereof
Evidence A No. 12: Journal of Clinical and Experimental Medicine, Vol. 96, No. 5, January 31, 1976, pages 288, 289, and 291
Evidence A No. 13: Kanzo, Vol. 21, No. 3, March 25, 1980, pages 303 to 304
Evidence A No. 14: Human cancer and Nude mouse, April 20, 1982, page 319
Evidence A No. 15: LONGMAN Advanced AMERICAN DICTIONARY, 2000, pages xviii to xix and pages 54 to 55
Evidence A No. 16: Journal of JAPAN ASSOCIATION FOR PRACTICAL ENGLISH, No. 15, September 2009, pages 29 to 38
Evidence A No. 17: An A-Z of English Grammar and Usage, 1996, pages 638 to 639
Evidence A No. 18: Intellectual property High Court case of 2012 (Ne) 10054, Brief on appeal on July 26, 2012 (Part 1: Patent Infringement Discussion), page 1, pages 47 to 48

3 Main Items described in Respective items of Evidence A

Note that the underlines of Respective items of Evidence A are added by the body. Further, the same can also apply to Respective items of Evidence B and the underlines added to the description of the specification.

(1) Matters described in A1

Note that the points are represented by page number and line number of A1, and the translation is made by the demandant.

(A1-1) "We wanted to determine whether the cleared mammary fat pad(s) (CFP) of the nude mouse would be as receptive to the growth of human mammary tissues, normal or neoplastic, as is the CFP of a normal mouse to syngeneic murine mammary tissues. If so, the site would be ideal for growth of human breast samples, and a model would be available for investigation of the growth potential of variously diseased human mammary tissues such as lobular carcinoma in situ, fibrocystic disease, and primary stage I carcinoma."
(page 1461, left column, lines 20 to 29)

(A1-2) "a human mammary tissue fragment was transplanted into each CFP."
(page 1461, left column, lines 38 to 40)

(A1-3) "Preparation of recipient gland-free mammary fat pads. The procedures described by Slemmer (4) were followed, all within a germfree isolator.
The #4 inguinal mammary fat pads of germfree female nude mice 20-25 days of age were cleared of host epithelium by surgical extirpation of the nipple rudiment and adjacent portions of the fat pad up to the site of the inguinal lymph node. When cleared in this manner, the mammary fat pads have been shown to completely lack any mammary epithelial outgrowth from the host." (page 1461, left column, line 50 to right column, line 3)

(A1-4) "Tissue for the fourth transplantation was obtained from a biopsy specimen of human breast tissue diagnosed as infiltrating ductal carcinoma (FIG. 9)." (page 1462, the right column, lines 23 to 25)

(A1-5) "Sections of the fat pad 2 months after transplantation showed the tumor to be healthy and beginning to infiltrate the fat pad (FIG. 10);" (page 1462, the right column,

lines 25 to 28)

(2) Matters described in A2
(A2-1) "Abdominal wall and intraperitoneal implantation were implemented by use of human cancer of stomach, and a histological search was conducted.

MATERIALS AND METHODS: Implantation into nude mouse (nu/nu-BALB/C/A/BOM, spf) by use of two cases of human cancer of the stomach.

Primary tumors of stomach cancer were all well-differentiated tubular adenocarcinoma. Implanted tumors were subcutaneous passage tumors of fourth passage to sixth passage, the others were primary tumors and subcutaneous passage tumors of second passage. Implanted tumors were cut up into a size of 5x5x5 mm, and implanted into an abdominal wall muscle layer, muscle layer-peritoneum, intraperitoneal, and gastric wall by a surgical procedure. Raising in a conventional condition, killed on a postoperative day 21 to 89 to discover a cancer infiltrative stage. ... (Omitted)...

Conclusion: There are already many reports of the possibility of subcutaneous passage of human stomach cancer in a nude mouse, but systematically few comparative experiments in the abdominal cavity. Subcutaneous passage tumors do not show localized growth or infiltration trend, but tumors were found within an abdominal wall muscle layer and in a peritoneum in the form of infiltration, adhesion to the peritoneum, the growth within pelvic cavity and gastric wall infiltration in the experimental method. The infiltration from serous surface to mucosa layer was observed particularly in a digestive tract. It seems to be of significance that an infiltrating image was obtained." (page 171, left bottom column, the item of "624", line 5 to last line).

(3) Matters described in A3
(A3-1) "Transplantation of human hepatoma to nude mice liver" (page 31, title)

(A3-2) "Animal bearing human cancer is an ideal model in studying biological properties of the tumor and various therapeutic effects. Implanted human cancer is required to have unchanged original nature in the host animal, and it is desirable to grow in an original organ." (page 31, left column, lines 1 to 5)

(A3-3) "Since then, attempts have been made to implant various human cancers into nude mice, and one of the authors has achieved a success in implanting pancreatic cancer[2)]. However, all of them are implanted in a subcutaneous tissue.

We have been mainly trying to implant into a nude mouse bearing hepatoma since 1976, and recently achieved a success in the transplantation of human hepatoma into a nude mouse liver for the first time, and thus report herein." (page 31, left column, lines 9 to 15)

(A3-4) "Experimental Methods

In eight cases of hepatoma for which our trauma unit conducted a surgery from October 1976 to July 1977, pieces of hepatoma tissue of three cases where excision was conducted, and four cases which only resulted in test excision were implanted. The mice used were male or female nude mice with a genetic background of BALB/C, which were supplied from Central Institute for Experimental Animals. ... (Omitted)...

The transplantation was conducted by cutting out a hepatoma tissue sampled by

excision or a needle into a piece of tissue with 2 mm square in saline, and transplanting this with a needle in both sides of abdominal region and dorsal region under the skin with the right side one being located close to a liver lateral segment." (page 31, left column, lines 16 to 28)

(A3-5) "Experimental result

Seven hepatoma tissues ever implanted were obtained from six cases with one case of hepatoblastoma and five cases of liver cells cancer. Three of six cases have taken and become capable of serial transplantation: the samples before and after chemotherapy for cirrhotic liver with hepatoma (Hc-3,4) of a 45-year-old male, differentiated hepatoma (Hc-5) of 70 year old male and hepatoblastoma (Hb-1) of a three-year-old male infant, which have been subcultured to sixth passage, second passage, and fourth passage, respectively." (page 31, left column, line 31 to right column, line 3)

(A3-6) "AFP value of Hc-4 was 8.2 μg/ml in patient's serum, and there are a positive one and a negative one in implanted rat by SRIA method. In the positive case, AFP values were detected only in the second and third passages of Hb-4, which were 10.1 μg/ml and 9 μg/ml, respectively." (page 31, the right column, lines 11 to 14)

(A3-7) "Remarkably, subcultured second passage rat formed a tumor mass with a size of about 1.5 cm as a result of the implantation of a piece of tumor mass into a liver at a deep region of a right flank region (FIG. 1). The tumor mass was a massive type, which had spread across the lobes with only a left lateral lobe being left. No ascites fluid or lymph node metastasis to hepatic portal region was observed, but a spherical metastasis with a diameter of about 2 mm was observed in the right lower lobe.

Histological appearance of tissue grown in a liver showed a thin fibrous capsule surrounding a tumor, and somewhat hemorrhagic, and a number of mitosis, differing from hypodermal tissue (FIG. 2).

The capsule of lung metastatic foci was only one layer of fibrous cells, and almost no reactive change was found in the surrounding lung tissue. The central part became the site of necrosis (FIG. 3)." (page 31, right column, line 18 to page 32, right column, line 7)

(A3-8) "FIG. 1 Human hepatocellular tumor implanted nude mice liver (cross sectional view) Tumor was partially bleeding and a massive type that had spread across the lobes except for the left lateral lobe." (page 31, FIG. 1)

(A3-9) "A Liver tumor before implantation B Tumor grown in a liver of nude mouse

H-E stain

FIG. 2 Histological observation (Hc-4)" (page 32, FIG. 2) (The body's note: the letters "A" and "B" are surrounded by circles.)

(A3-10) "FIG. 3 Histological Observation (Hc-4) lung metastatic foci H-E stain" (page 32, FIG. 3)

(A3-11) "Conventionally, a subdermal region of dorsal region or lower extremity, etc. is used for an implanted site. These sites might change a type of reaction of surrounding tissue of tumor from an original organ. Specifically, hepatocellular tumor grown under the skin usually shows a spherical shape covered with a relatively thick fibrous capsule, but almost no fibrous capsule formation in our case of liver transplantation, bleeding in some region, somewhat differing from a manner grown under the skin, and furthermore involves lung metastasis.

Most of the reports did not recognize metastasis in a nude mouse transplantation of human tumor[5)-8)], whereas there are only a few reports of metastasis from Nagai[9)]. Microscopic metastatic foci has been found in local nodes for the case of subcultured second passage hepatocellular tumor, but there is no report of the case of lung metastasis." (page 32, right column, line 26 to page 33, left column, line 10)

(A3-12) Human tumor implanted in a nude mouse showed almost no metastasis. This is supposed to be because of being the animal with immune deficiency, a change of biological nature of implanted tumor, or a death prior to metastasis due to a few case of long-term survival since it was not conducted under SPF environment. One possible major factor may be that the implanted site was a hypodermal tissue. Specifically, if implanted in an original organ, it might possibly show a similar metastasis. We would like to believe that the induction of lung metastasis by our liver-implanted hepatocellular tumor had clearly demonstrated this." (page 33, left column, lines 11 to 19)

(A3-13) "Summary

We have report the successful transplantation of human hepatoma in nude mouse. Somewhat differing in a manner of growing from the one implanted subcutaneously, no fibrous capsule of tumor was found, but the metastasis to the lung was observed." (page 33, the right column, lines 1 to 4)

The body's note: Typographical error of A3

A3 discloses that "Remarkably, a subcultured second passage rat formed a tumor mass with a size of about 1.5 cm as a result of the implantation of a piece of tumor mass into a liver at a deep region of a right flank region (FIG. 1). ... (Omitted)... a spherical metastasis with a diameter of about 2 mm was observed in the right lower lobe.

Histological appearance of tissue grown in a liver showed a thin fibrous capsule surrounding a tumor, and somewhat hemorrhagic, and a number of mitosis, differing from that of hypodermal tissue (FIG. 2)." (A No. 3-7), which describes rat.

FIG. 1 (A3-8) cited herein describes, however, "FIG. 1 Human hepatocellular tumor implanted nude mice liver (cross sectional view)." FIG. 2 (A3-9) cited herein describes "Tumor grown in a liver of nude mouse." In view of this, the target for implantation is a nude mouse.

Furthermore, as a summary of the article of A3, it describes that "We have report the successful transplantation of human hepatoma in nude mouse. Somewhat differing in a manner of growing from the one implanted subcutaneously, no fibrous capsule of tumor was found, but the metastasis to the lung was observed." (A3-13) It can be seen from this that nude mouse is a target for implantation.

Taking all the above into account, "rat" of (A3-7) is construed as an obvious

typographical error of mouse.

(4) Matters described in A4
(A4-1) "A method of cellular culture or animal implantation is used for studying biological characteristics of human tumor or various anticancer study, but these methods are not always feasible depending on kinds of tumors. ... (Omitted)... In particular, animal bearing human cancer is an ideal model in studying biological properties of the tumor and various therapeutic effects. Implanted human cancer is required to have unchanged original nature in host animal." (page 303, left column, lines 2 to 11)

(A4-2) "On the other hand, the studies of human hepatoma have been conducted by a clinical study and animal-generated hepatoma due to the difficulty of the establishment of the cell cultivated strain." (page 303, left column, line 20 to right column, line 2)

(A4-3) "From such a viewpoint, the author implants human hepatoma into a nude mouse to attempt its succession. At this time, the first passage succession implantation system could have been established. Accordingly, we report the finding obtained by a consideration given to the biological characteristics of human hepatoma implanted in a nude mouse and the appropriateness for the subject of human hepatoma study as well as the other 14 cases in which a serial transplantation was conducted but a systematization failed." (page 303, the right column, lines 3 to 8)

(A4-4) "1. Experimental Animals
Male and female BALB/c nude mouse (nu/nu) raised under a specific pathogen free condition in Central Institute for Experimental Animals at 5 to 7 weeks old were used." (page 303, the right column, lines 10 to 13)

(A4-5) "2. Experimental Methods
Hepatoma patients were sixteen cases who were hospitalized in First Surgery Department of Hokkaido University and underwent laparotomy from November 1976 to May 1978, of which there were 14 cases in which 15 pieces of liver tumor tissue implantable into a nude mouse were sampled from surgical or excised specimen. These tissue pieces were subjected to primary implantation into a nude mouse, and tissue samples taken were further subjected to serial transplantation.
... (Omitted)...
Note that the implantation system is described as Hc for hepatocellular tumor, Hb for hepatoblastoma, which are respectively numbered in the order of implantation." (page 303, right column, line 19 to page 304, line 9)

(A4-6) "(a) Primary implantation
A hepatoma tissue was aseptically sampled by from the partial excision of tumor or from a liver excision sample, and this was cut out in a 2 mm square or less after removing a necrotic zone and a blood constituent in saline by use of a knife and a pincette. Subsequently, one or several pieces of the tissue were implanted subcutaneously into a lateral region or a dorsal region of a nude mouse by use of a needle." (page 304, left column, lines 11 to 17)

(A4-7) "(b) Serial transplantation

When tumors that had undergone first passage or serial transplantation reached a certain size, the nude mouse was cardiopunctured under anesthesia with ether, followed by blood drawing, and then tumors were aseptically isolated. This tumor was immediately put into a physiological saline, and cut out into about 2 mm square, and one or several pieces thereof were implanted subcutaneously into a lateral region or a dorsal region of another new nude mouse by use of a needle. ... (Omitted)...

These serial transplantations were conducted at a time point when a diameter exceeds about 1 cm, where the bleeding, central necrosis and exulceration of tumor rarely took place." (page 304, left column, lines 23 to 33)

(A4-8) "(c) Transplantation into nude mouse liver

Nude mouse was opened under anesthesia with ether, and a piece of tissue with 1 to 2 mm square prepared by the aforesaid method was implanted into a liver middle lobe by use of a needle with an outer diameter of 2.5 to 1.5 mm. Further, a needle was inserted into a right flank region of nude mouse subcostally, so that a piece of tumor tissue might contact with liver right lateral segment." (page 304, left column, lines 34 to 39)

(A4-9) "It was 10 which were subjected to the subcostal insertion of a needle into a right flank region of nude mouse to implant into a liver, but it was only two of the second passage of Hc-3 and the third passage of Hc-5 that made a success. Implantation into a liver was conducted by opening the abdominal cavity for two of the sixth passages of Hc-4. Both have taken, but one has gotten wasting disease 18 days after implantation, another 38 days after implantation, and both have been killed. After killing four, the presence of hepatoma was observed. Further, a lung metastasis was observed in the second passage of Hc-3 implanted into a right subcostal region[27)]." (page 306, left column, lines 16 to 23)

(A4-10) "Six cases that established the primary implantation were all subcultured, and all cases achieved success in the second passage implantation, and the serial transplantation was further continued" (page 306, right column, lines 1 to 2)

(A4-11) "Further, it is interesting that the direct implantation into a liver showed an AFP value 10 times higher than the other one. The correlation between the tumor occurrence origin and the AFP value should be considered hereinafter. It is assumed that there are some differences in terms of take rate and biological characteristics of implanted tumor between subcutaneous implantation and implantation into liver of hepatoma." (page 312, left column, lines 26 to 31)

(A4-12) "Fifteen tumor tissues sampled from fourteen cases were subjected to serial transplantation into nude mice. As a result, the following conclusion was obtained. 1) Primary implantation achieved success in five cases of thirteen cases for hepatocellular tumors, and one case of two cases for hepatoblastoma. ... (Omitted)... 4) AFP was detected from all six cases that took. 5) Implanted hepatocellular tumor showed an image analogous to an original tumor, except that the alveolar formation was not significant. 6) Metastasis was observed in only one where an infiltrative tumor was

formed in a liver, which was a lung metastasis. 7) Karyotype analysis, serum absorption test, and precipitation reaction caused by anti-human AFP serum, etc. identified the lung metastasis as of a human origin." (page 312, the right column, lines 4 to 18)

(A4-13) "The document '27)' is 'Junichi UCHINO, Takehiko KUWAHARA and others: Implantation into a nude mouse of human hepatoma, Journal of Clinical and Experimental Medicine, 104:31, 1978.'" (page 313, right column)

(A4-14) "3) Macroscopic findings

After removing a tumor for serial transplantation, necropsying a deceased one due to another cause, the nature of a tumor and the presence or the absence of distant metastasis, etc. were observed macroscopically." (page 304, the right column, lines 13 to 16)

(A4-15) Table 1 on page 305 discloses hepatoma to be implanted in a nude mouse as Hc-3 of 45 year old male before chemotherapy obtained by a centesis biopsy.

No. 3 The demandee's allegation

1 Object of the reply

The demandee seeks for the trial decision to the effect that the demand for trial should be dismissed, and the costs in connection with the trial shall be borne by the demandant, and submits the following Evidence B No. 1 to B No 73-2, and counter-argues that the demandant's allegation of reasons for invalidation are groundless and the patents according to the Invention should not be invalidated under the provision of Article 123(1) of the Patent Act.

2 Means of Proof

Evidence B No. 1: MEDICAL REVIEW CO., LTD., Stedman's Medical Dictionary 3rd Edition, Fifth print, March 10, 1995, pages 630 to 631

Evidence B No. 2: Jikken Igaku Bessatsu BioScience Term library Immunology, YODOSHA CO., LTD., First print, November 1, 1995, pages 14 to 17

Evidence B No. 3: Jikken Igaku Bessatsu BioScience Term library Immunology, YODOSHA CO., LTD., First print, November 1, 1995, pages 18 to 19

Evidence B No. 4: English-Japanese Dictionary, Kenkyusha Co., Ltd., 28th Print, 1997, pages 866 to 867

Evidence B No. 5: Edited by Science editorial desk, additional volume: Science Cancer, NIKKEI SCIENCE Inc., November 20, 1981, pages 98 to 110

Evidence B No. 6: Edited by Ikuop Saiki and Takashi Aikoh, "Experimental method of cancer metastasis study", KINPODO, INC., First Edition, First Print, August 1, 2008, pages 8 to 11

Evidence B No. 7: MEDICAL REVIEW CO., LTD., Stedman's Medical Dictionary 3rd Edition, Fifth print, March 10, 1995, pages 738 to 739

Evidence B No. 8: MEDICAL REVIEW CO., LTD., Stedman's Medical Dictionary 3rd Edition, Fifth print, March 10, 1995, pages 752 to 753

Evidence B No. 9: Edited by Ikuo Saiki and Takashi Aikoh, "Experimental method of cancer metastasis study", KINPODO, INC., First Edition, First Print, August 1, 2008, pages 24 to 28

Evidence B No. 10: Cancer Res., vol.48, December 1, 1988, pp. 6863 to 6871, and the translation thereof
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3 Main Items described in Respective items of Evidence B

The translation of Evidence B No. 57-1 is based on the translation submitted as Evidence B No. 57-2 attached to the written statement on July 30, 2013 from the demandee. The page number and the line number respectively correspond to the page number and the line number of the original text. Further, the translations of the other respective items of Evidence B are also based on the translations submitted by the demandee.

(1) Evidence B No. 57-1

(B57-1-1) "Materials and Methods

Mice. Four-week-old outbred nu/nu mice of both sexes were used for tumor

implantation. All animals were maintained in a sterile environment." (page 9345, the right column, lines 17 to 20)

(B57-1-2) "Colon Cancer Specimens. Fresh surgical specimens were obtained as soon as possible, but no later than 24 hr after surgery, from local San Diego hospitals and kept in Earl's minimal essential medium (MEM) at 4°C." (page 9345, the right column, lines 25 to 28)

(B57-1-3) "Results and Discussion

Twenty different cases of colon cancer surgical specimens were implanted orthotopically, directly or with the use of gelfoam, an internal skin flap with gelfoam." (page 9346, left column, line 6 from the bottom to last line)

(B57-1-4) "Local Growth and Abdominal Metastasis. An example is specimen case 1701, an infiltrating mucinous adenocarcinoma of the right colon (modified Duke's classification*2 C2). Two nude mice with preimplanted gelfoam were used for tumor implantation, two nude mice were used for tumor implantation with an internal skin flap, and two nude mice were used for direct implantation of tumor tissue to the cecum. Two of the six mice suffered early death (one with direct tumor implantation, one with gelfoam preimplantation) and were not available for assessment of tumor growth. All of the remaining mice demonstrated extensive*3 primary growth ranging from 8 mm x 5.7 mm to 13 mm x 13 mm as well as abdominal-wall metastases ranging from 8 mm x 11 mm to 22 mm x 15 mm. All of the remaining mice showed visible tumor growth in the abdomen. Autopsies were performed 113-139 days after implantation." (page 9346, the right column, lines 8 to 23)

(B57-1-5) "Local Growth, Abdominal Metastasis and Lymph-node metastases. An example is specimen case 1707, an infiltrating adenocarcinoma of the right colon, moderately differentiated (modified Duke's classification D). ... (Omitted)... In the mouse with direct tumor implantation and in the other mouse with coimplantation of tumor and normal surrounding tissue, only local tumor growth occurred when observed at autopsy on days 159 and 230 after implantation, respectively." (page 9346, right column, line 24 to page 9347, left column, line 16)

(2) Evidence B No. 69-1
(B69-1-1) "A new patient-like metastatic model of human lung cancer constructed orthotopically with intact tissue via thoracotomy in immunodeficient mice" (page 992, title)

(B69-1-2) "Table I shows that when poorly-differentiated large-cell-squamous-cell tumor 2268 was transplanted orthotopically to the left lung as histologically-intact tissue directly from surgery, 5 out of 5 mice produced locally-grown tumors averaging 8.2 mm in diameter, in an average time of 61 days. Opposite-lung metastases occurred, as well as lymph-node metastases (Table I)." (page 992, the right column, lines 43 to 49)

(3) Evidence B No. 71-1
(B71-1-1) "Materials and Process

Four-week-old outbred nu/nu mice of both sexes were used for tumor implantation. ... (Omitted)... A surgical specimen of a poorly-differentiated ductal carcinoma of human breast (Anticancer #2468) was used for tumor transplantation." (page 901, the right column, lines 22 to 28)

(B71-1-2) Results and Discussion

Eight mice were used for orthotopic transplantation and seven mice were used for subcutaneous transplantation of the breast cancer specimen. All 15 mice had primary tumor growth after transplantation. The subcutaneously-growing tumors were encapsulated with no local invasion or distal organ metastatis observed. For mice with orthotopic transplantation, the local tumor grew in the mammary gland into a very large mass (Figure 2). The locally-growing tumor was anaplastic and poorly differentiated (Figure 1B) and was very similar to the pretransplantation patient's tumor (Figure 1A). No local invasion and infiltration of the tumor, and no axillary lymph node metastasis were observed. However, six out of eight (75%) mice in the orthotopic transplantation group had multiple metastatic nodules in the lung (Table I, Figure 1C)." (page 904, left column, lines 11 to 26)

(4) Evidence B No. 72-1

(B No. 72-1-1) "Materials and Process

Animals Three-week-old outbred nu/nu mice (female) were used for tumor implantation. ... (Omitted)... Access to tissue. A fresh chest lining was obtained from sidewall chest lining of 65 year old white female. This female had a sustained relapsing pleural effusion of right lung and a secondary metastatic ovarian cancer in the ovary." (page 1999, right column, line 7 from the bottom to page 2000, left column, line 3)

(B72-1-2) page 2000, Table 1

"Table I Local growth of human chest lining adenocarcinoma after orthotopic implantation into a nude mouse as an intact tissue

		Metastasis of tumor			
Implantation	Local growth	Chest wall	Ipsilateral lung	Mediastinum	Lymph nodes in the mediastinum
Sidewall chest lining	3/3[1]	3/3	1/3	1/3	0/3
Visceral chest lining	3/3	2/3	3/3	3/3 [2]	2/3

[1] Number of mice bearing tumor/Number of mice implanted

[2] Include lesion of pericardial sac

No. 4 The Invention

The inventions according to Claims 1 to 19 (Hereinafter referred to 'the Inventions 1 to 19'; further, the inventions 1 to 19 are collectively referred to as 'the patent invention') are the inventions relating to "ANIMAL MODEL FOR HUMAN DISEASE", as specified by the following matters recited in Claims 1 to 19 of the scope of the claims corrected by the request for correction on March 30, 1999. (See the

Appendix of the trial decision)
[Claim 1] A non-human animal model for the metastasis of human neoplastic disease, said animal having a neoplastic tissue obtained from a human organ, other than brain, implanted into the corresponding organ of said animal, having sufficient immunodeficiency to allow said implanted neoplastic tissue to grow and metastasize.
[Claim 2] An animal model according to claim 1, wherein said animal is an athymic mouse.
[Claim 3] An animal model according to claim 2, wherein said human neoplastic tissue is obtained from the human liver, kidney, stomach, pancreas, colon, breast, prostate, lung, or testis.
[Claim 4] An animal model according to claim 3, wherein said neoplastic tissue is obtained from human kidney.
[Claim 5] An animal model according to claim 4, wherein said human neoplastic kidney tissue is implanted in the renal cortex of the kidney of the mouse.
[Claim 6] An animal model according to claim 3, wherein said neoplastic tissue is obtained from a human stomach.
[Claim 7] An animal model according to Claim 6, wherein human neoplastic stomach tissue is implanted in the stomach of the mouse between the inner mucosal lining of the stomach and the outer peritoneal coat of the stomach.
[Claim 8] An animal model according to claim 3, wherein said neoplastic tissue is obtained from human colon.
[Claim 9] An animal model according to claim 8, wherein said neoplastic stomach tissue is implanted in the cecum of the large intestine of the mouse.
[Claim 10] A female animal model according to claim 3, wherein said neoplastic tissue is obtained from a female human breast.
[Claim 11] A method of generating a non-human animal model for the metastasis of human neoplastic disease, said method comprising: providing a laboratory animal having sufficient immunodeficiency to allow implanted human neoplastic tissue to grow and metastasize in said animal; and implanting a specimen of neoplastic tissue from a human organ other than brain into the corresponding organ of the immunodeficient animal.
[Claim 12] A method according to claim 11, wherein said laboratory animal is an athymic mouse.
[Claim 13] A method according to claim 12, wherein said human neoplastic tissue is obtained from the human liver, kidney, stomach, pancreas, colon, breast, prostate, lung, or testis.
[Claim 14] A method according to claim 13, wherein said neoplastic tissue is obtained from human kidney.
[Claim 15] A method according to claim 14, wherein said human neoplastic kidney tissue is implanted in the renal cortex of the kidney of the mouse.
[Claim 16] A method according to claim 13 wherein said neoplastic tissue is obtained from human stomach.
[Claim 17] A method according to claim 16, wherein said human neoplastic stomach tissue is implanted in the stomach of the mouse between the inner mucosal lining of the stomach and the outer peritoneal coat of the stomach.
[Claim 18] A method according to claim 13, wherein said neoplastic tissue is obtained from human colon.

[Claim 19] A method according to claim 18, wherein said neoplastic colon tissue is implanted in the cecum of the large intestine of the athymic mouse."

No. 5 Construction of Inventions 1 to 19

(1) Construction of "a neoplastic tissue obtained from human organ" of Inventions 1 to 10

The scope of claims of Inventions 1 to 10 only describes a "neoplastic tissue obtained from human organ." The definition of this could be found neither herein nor in the whole disclosure of the whole text of the Corrected specification (hereinafter referred to as "the specification") corrected by the request for correction on March 30, 1999 attached to the Appendix.

Here, when it comes to the column of "Detailed Description of the Invention" of the specification, there are the following descriptions:

(The specification-1) "the human neoplastic tissue utilized herein comprises tissue from fresh surgical specimens which are pathologically diagnosed tumors occurring in, for example, human kidney, liver, stomach, pancreas, colon, breast, prostate, lung, testis, and brain." Such tumors include carcinomas as well as sarcomas, and implantation thereof as carried out herein encompasses all stages, grades and types of tumors. Further, human neoplastic tissue used is implanted in a lump without separating individual cells. A three-dimensional structure of a tumor tissue may be maintained by implanting a lump of the tumor tissue. Therefore, a human tumor animal model with higher reliability may be obtained." (The specification, page 4, lines 13 to 20)

(The specification-2) "The present invention relates to a non-human animal model for human neoplastic disease. More particularly, the invention relates to a non-human animal model having neoplastic tissue, obtained from a human organ, implanted into the corresponding organ of the animal." (The specification, page 2, lines 18 to 20)

(The specification-3) "having neoplastic tissue obtained from a human organ implanted into the corresponding organ of the animal" (the specification, page 3, lines 24 to 25)

(The specification-4) "a specimen of neoplastic tissue from a human organ" (the specification, page 3, line 29)

(The specification-5) "implantation of human neoplastic tissue" (the specification, page 4, line 4)

(The specification-6) "Prior to implantation, the human neoplastic tissue is maintained by placing in a suitable nutrient medium, such as Eagle's minimum essential medium containing ten percent fetal calf serum and a suitable antibiotic, such as gentamycin. The medium containing the tissue is then cooled to approximately about 4C. The tissue can be maintained in this manner for approximately twenty-four hours." (The specification, page 4, lines 21 to 24)

Further, in the examples of the column of "Detailed Description of the Invention" of the specification, a neoplastic tissue obtained from a human organ has been directly implanted into the corresponding organ of the animal (the specification, page 7 and later). Further, the specification also discloses that "The placement of neoplastic tissue in an immunodeficient laboratory animal according to the present invention is carried out by means of orthotopic implantation. ...

(Omitted)... In the present invention, the terminology orthotopic implantation is used to refer to the grafting of human neoplastic tumor tissue from a human organ into the

corresponding organ of an immunodeficient laboratory animal." (The specification, page 4, lines 10 to 13).

All the above description relates to a lump of neoplastic tissue sampled from a human organ. The passage of this to the other animal is not mentioned.

In view of these points, it is reasonable to understand that the "neoplastic tissue from a human organ" is the very same neoplastic tissue sampled from a human organ. Further, if the neoplastic tissue is this sort of thing, it can be said as a matter of course that "a three-dimensional structure of a tumor tissue may be maintained."

(The demandee's allegation)

Further, the demandee argues as follows:

Allegation 1: "the human neoplastic tissue utilized herein comprises tissue from fresh surgical specimens which are pathologically diagnosed tumors occurring in, for example, human kidney, liver, stomach, pancreas, colon, breast, prostate, lung, testis, and brain." Regarding (The specification-1), the term 'fresh' corresponds to the term 'fresh' of the specification of the international filing date, and means 'a fresh specimen tissue'; i.e., a tissue that is not in a frozen state, and thus it does not mean 'the very same tissue (obtained from surgery)'". (Written reply, page 18, lines 7 to 9 and Written reply, page 17, the item of "(2-4) The item of "fresh specimen tissue")

Allegation 2: If the "fresh specimen tissue" is construed as the very same tissue (obtained from surgery)" in a strict sense, such a tissue may not be implanted. Because as a matter of course, not only a tumor tissue but also the surrounding tissue, blood and lymph fluid etc. are attached to the tumor tissue isolated for implantation, and it is necessary to process the isolated tissue into a proper size for implantation. (Written reply, page 18, lines 10 to 14)

Allegation 3: "the human neoplastic tissue utilized herein comprises tissue from fresh surgical specimens ..., for example, human ..." In the description of (The specification-1), the term "from" means "derived from" on the grounds of the description of the specification of the international filing date. (Written reply, page 18, last line to page 19, line 3 and Written reply, page 16, the item of "(2-3) The item of 'obtained from a human organ other than brain'")

Specifically, Allegation 1 and Allegation 3 are based on the description of the specification of the international filing date. However, pursuant to the provision of Article 184-4(4) of the Patent Act before revision, of which the provisions then in force shall remain applicable according to revision supplement Article 7 of Heisei 6-nen Law No. 116, the matters that are not described in the translation as of the expiration of Deadline of National Phase Entry but are described in the specification or the scope of claims of International Patent Application as of the International filing date are deemed to be not described in the specification or the scope of claims of International Patent Application as of the International filing date. Therefore, the description of the specification of the International filing date cannot be a ground for the construction of the specification.

Further, the demandee argues in Allegation 2 that, if the "fresh specimen tissue" is construed as the very same tissue (obtained from surgery)" in a strict sense, such a tissue may not be implanted. Indeed, it is obvious to implement any treatment necessary for implantation such as cleaning, but the treatment of subjecting a nude

mouse to subcutaneous passage is not a means ordinarily practiced in implantation such as a cleaning, etc. It cannot be seen that the subcutaneous passage is included into a treatment necessary for implantation.

Additionally, in the description of "the human neoplastic tissue utilized herein comprises tissue from fresh surgical specimens which are pathologically diagnosed tumors occurring in, for example, human kidney, liver, stomach, pancreas, colon, breast, prostate, lung, testis, and brain." (The specification-1), the term "for example" exemplifies the organs following kidney. Thus it cannot be construed that the "fresh specimen tissue" is regarded as an example encompassed into "human neoplastic tissue."

(2) "Neoplastic tissue obtained from human organ" of Inventions 11 to 19

Further, for a similar reason to the above "(1)," it is reasonable to understand that the "neoplastic tissue from a human organ" is the very same neoplastic tissue itself sampled from a human organ.

No. 6 Problem to be solved by the Invention, technical significance, objective, and effects of Inventions 1 to 19 to be recognized from the specification

The specification has the following descriptions with regard to the problem to be solved, technical significance, objective, and effects:

(The specification-7) "BACKGROUND OF THE INVENTION

The present invention relates to a non-human animal model for human neoplastic disease. More particularly, the invention relates to a non-human animal model having neoplastic tissue, obtained from a human organ, implanted into the corresponding organ of the animal." (The specification, page 2, lines 17 to 20)

(The specification-8) "There has long been a need for a representative animal model for human neoplastic disease. Such a model could serve many purposes. For example, it could be used to study the progression of neoplastic disease in humans and assist in finding appropriate treatment forms. Such a model could also be used to test the efficacy of proposed new anti-neoplastic agents. Additionally, it could be employed in individualized chemosensitivity testing of cancer patients' tumors. The existence of such an animal model would make drug screening, testing, and evaluation much more efficient and much less costly." (The specification, page 2, lines 21 to 27)

(The specification-9) "Some previous attempts at generating animal models for human neoplastic disease employed transplantable animal tumors. These were tumors that had developed in rodents and had been transplanted from animal to animal, usually in inbred populations. Other animal tumor models were generated by inducing tumors in the animals by means of various agents that were carcinogenic, at least in the animal system. Still other animal tumor models were rodents containing spontaneously occurring tumors. These rodent models, however, frequently responded to chemotherapeutic agents very differently than human subjects receiving the same agent." (The specification, page 2, line 28 to page 3, line 5)

(The specification-10) "Another animal tumor model that developed starting some twenty years ago utilized mice without a thymus. These animals were deficient in cellular aspects and therefore lost their ability to reject foreign transplant tissue. The mice, for reasons not clearly understood, were essentially lacking in hair and came to be

called "nude" or "athymic" mice. It was found that human tumors often grew when implanted subcutaneously under the skin of these nude mice. However, the take rate or frequency with which such human tumor tissue actually formed a tumor in the mouse varied depending on the individual donor and the tumor type. In these models, tumors that took often grew to a great extent at the site of implant and rarely metastasized, even if the original tumor had been highly metastatic in the donor. Accordingly, the subcutaneous nude mouse human tumor model, although better than the previously described rodent model, still had a substantial drawback; i.e., the subcutaneous transplant lacked the ability to metastasize.

To fulfill the need for an animal model for human neoplastic disease which is without the above-mentioned deficiencies, the present invention discloses a new animal model which has the ability to truly mimic the progression of neoplastic disease as it occurs in humans." (The specification, page 3, line 6 to page 3, line 20)

(The specification-11) "SUMMARY AND OBJECT OF THE INVENTION

It is the primary object of the present invention to provide an improved non-human animal model for human neoplastic disease. In accordance with the primary aspect of the present invention, a novel non-human animal model for human neoplastic disease is provided having neoplastic tissue obtained from a human organ implanted into the corresponding organ of the animal and having sufficient immunodeficiency to allow the implanted tissue to grow and metastasize. Another aspect of the invention provides a method of generating an non-human animal model for human neoplastic disease, the method comprising, providing a laboratory animal having sufficient immunodeficiency to allow implanted human neoplastic tissue to grow and metastasize in said animal, and implanting a specimen of neoplastic tissue from a human organ into the corresponding organ of the immunodeficient animal." (The specification, page 3, line 21 to page 4, line 1)

(The specification-12) "The animal model of the present invention is generated by implantation of human neoplastic tissue into a laboratory animal having sufficient immunodeficiency to allow the implanted tissue to grow and metastasize." (The specification, page 4, lines 3 to 4)

(The specification-13) "The placement of neoplastic tissue in an immunodeficient laboratory animal according to the present invention is carried out by means of orthotopic implantation. This refers to an implant or graft transferred to a position formerly occupied by tissue of the same kind. In the present invention, the terminology orthotopic implantation is used to refer to the grafting of human neoplastic tumor tissue from a human organ into the corresponding organ of an immunodeficient laboratory animal. The human neoplastic tissue utilized herein comprises tissue from fresh surgical specimens which are pathologically diagnosed tumors occurring in, for example, human kidney, liver, stomach, pancreas, colon, breast, prostate, lung, testis, and brain. Such tumors include carcinomas as well as sarcomas, and implantation thereof as carried out herein encompasses all stages, grades, and types of tumors. Further, human neoplastic tissue used is implanted in a lump without separating individual cells. A three-dimensional structure of a tumor tissue may be maintained by implanting a lump of the tumor tissue. Therefore, a human tumor animal model with higher reliability may be obtained." (The specification, page 4, lines 10 to 20)

(The specification-14) "The animal models of the present invention are particularly useful in studying the progression of human neoplastic disease. These studies, in

combination with other clinical testing modalities such as diagnostic imaging, help in the selection of the most appropriate form of treatment.

For example, when an animal model of the present invention is subjected to tumor imaging, the clinician is allowed to identify both primary and secondary sites of tumor growth and to estimate the overall burden of the tumor on the animal. Tumor imaging is conventionally carried out by injecting the animal with a labeled anti-tumor antibody such as an antibody labeled with a radioactive isotope; allowing the antibody time to localize within the tumor; and then scanning the animal using a radiation detector. When a computer is used to compile an image of the radioactivity detected in the animal's body, the computer can color code the image according to the intensity of the radiation. Zones of high radioactivity in regions of the body not expected to accumulate the antibody or its metabolites indicate the possible presence of tumors.

The animal models of the present invention can also be used to screen new antineoplastic agents to determine the ability of such agents to affect tumors at the primary site and also at distant metastatic sites or to prevent distant metastases from occurring. The models will be also useful for individualized chemosensitivity testing of a cancer patient's tumors.

Additionally, the animal models of the present invention are useful in studying the effects of mitrution on the progression of human neoplastic disease.
These studies can be particularly significant in view of the demonstrated impact of various deficiencies on healthy subjects." (The specification, page 6, line 20 to page 7, line 8)

(The specification-15) "EXAMPLE I

Fresh surgical specimens of tissue from a tumor excised from a human kidney were transplanted into the kidneys of five animal recipients. The tissue specimens, which were pathologically diagnosed as renal cell carcinoma, were prepared to size by the teasing procedures described earlier. Five athymic nude mice age four (4) to six (6) weeks were selected as the animal recipients for the implants.

... (Omitted)...

An incision was made in each animal to access the kidney. A wedge shaped cavity was formed by excision of the renal cortex of each recipient kidney, and a mass of tumor tissue of approximately 0.5 x 0.2 cm was placed in the defected cavity. A mattress suture was then employed to secure the implant in place.

The five mice of this example are still alive six months later. Approximately one month following implantation of the tissue, the mice were surgically opened and the implanted tumors were observed. In each case, the tumor was found to have taken. This means that the implanted neoplastic tissue had invaded adjacent tissue. ... (Omitted)...

Histological analysis revealed that the tissue in the recipient animals (1) preserved its architecture and tissue type and (2) mimicked progression of the disease in the human donor." (The specification, page 7, line 9 to page 7, last line)

(The specification-16) "EXAMPLE II

Specimens of human tissue excised from the stomach and pathologically diagnosed as gastric carcinoma were prepared to size by the teasing procedure described earlier.

Five athymic nude mice age four (4) to six (6) weeks were selected as the animal recipients for the implants. ... (Omitted)...

Each anesthetized mouse was opened to provide access to the stomach. An incision was made in the stomach wall using a number 11 scalpel while taking care not to penetrate the mucosal layer. A pocket was formed large enough to receive a tumor mass of about 0.5 x 0.2 cm. A tumor of approximately this size was selected and inserted into the pocket and the incision was closed using a 7-0 suture.

The five mice of this example have survived for about three (3) to four (4) months and otherwise appear healthy. Subsequent surgical opening of the stomach of these mice has verified that the tumors have taken." (The specification, page 8, lines 1 to 12)

(The specification-17) "EXAMPLE III

Specimens of human tissue removed from a human colon and pathologically diagnosed as colon carcinoma were prepared to size by the teasing procedure described earlier. Five athymic nude mice, age four (4) to six (6) weeks, were selected as the animal recipients for the implants. ... (Omitted)...

Each anesthetized mouse was opened to provide access to the colon. ... (Omitted)... A selected tumor mass of approximately 0.5 x 0.2 cm was inserted into the pocket which was then closed with a suture.

Four of the five mice which underwent this implant surgery have survived for three to four months and appear to be in good health. Approximately one month following tissue implantation, the mice were surgically incised and the tumors were observed to have taken. None of the tumors appeared not have metastasized to other organs at this time." (The specification, page 8, line 13 to 24)

Comprehensively taking into consideration the matters recited in the scope of claims of Inventions 1 to 19 and described in the above specification, the following "Problem to be solved by Inventions 1 to 19," "technical significance of Inventions 1 to 19,", "objective of Inventions 1 to 19," and "effects of Inventions 1 to 19" can be recognized.

1 Problem to be solved by Inventions 1 to 19

It can be seen that there is conventionally a problem to prepare an animal model for human neoplastic disease which has the ability to truly mimic the progression of neoplastic disease as it occurs in humans; i.e., an animal model for human neoplastic disease with an ability sufficient to metastasize and grow human neoplastic tissue; although an animal model without a thymus and the ability to reject foreign transplant tissue (nude mice, athymic mice, athymic nude mice) brought a better result than an animal model of rodent animal, it showed a varied take rate or frequency with which such human tumor tissue actually formed a tumor in the mouse depending on the individual donor and the tumor type, and had a substantial drawback of tumors that took growing to a great extent at the site of implant and being rarely metastasized, even if the original tumor had been highly metastatic in the donor; i.e., the subcutaneously transplanted human tumor tissue lacked the ability to metastasize.

2 Technical meaning of Inventions 1 to 19

It can be seen that the technical significance of Inventions 1 to 19 lies in that a non-human animal model has been prepared and provided so as to have the ability to truly mimic the progression of neoplastic disease as it occurs in humans; i.e., a non-

human animal model for metastasis with a human tumor tissue that can metastasize and grow, by maintaining a "three-dimensional structure" of a lump of an original tumor tissue without separating individual cells from a human tumor tissue obtained from a human organ other than brain and implanting (orthotopic implantation) the tissue in a corresponding organ of an immunodeficient animal.

3 The object of Inventions 1 to 19

It can be seen that the objective of Inventions 1 to 19 lies in the preparation of an animal model which has the ability to truly mimic the progression of neoplastic disease as it occurs in humans; i.e., an animal model for human neoplastic disease with an ability sufficient to metastasize and grow human neoplastic tissue to try to solve the above "1 Problem to be solved by Inventions 1 to 19."

4 Effects of Inventions 1 to 19

It can be seen that the objective and the effects of Inventions 1 to 19 lie in that a non-human animal model has been prepared and provided so as to have the ability to truly mimic the progression of neoplastic disease as it occurs in humans; i.e., a non-human animal model for metastasis with a human tumor tissue that can metastasize and grow, by maintaining a three-dimensional structure of a lump of an original tumor tissue without separating individual cells from a human tumor tissue obtained from a human organ other than brain and implanting (orthotopic implantation) the tissue in a corresponding organ of an immunodeficient animal (nude mice, athymic mice, athymic nude mice).

No. 7 Reasons for invalidation 1 (Violation of Article 29(1), main paragraph of the Patent Act)

1 Description of the specification

The specification has the following descriptions of Examples relating to metastasis.

"Example III

Specimens of human tissue removed from a human colon and pathologically diagnosed as colon carcinoma were prepared to size by the teasing procedure described earlier. Five athymic nude mice, age four (4) to six (6) weeks, were selected as the animal recipients for the implants. In preparation for surgery, the mice were anesthetized with ether.

Each anesthetized mouse was opened to provide access to the colon. A pocket of cavity was surgically formed in the seromuscular layer with care exercised not to enter the lumen. A selected tumor mass of approximately 0.5 x 0.2 cm was inserted into the pocket, which was then closed with a suture.

Four of the five mice which underwent this implant surgery have survived for three to four months and appear to be in good health. Approximately one month following tissue implantation, the mice were surgically incised and the tumors were observed to have taken. None of the tumors appeared not to have metastasized to other organs at this time." (The specification, page 8, lines 13 to 24)

2 Matter to be recognized from Example III

(1) Implanted neoplastic tissue

The tissue to be implanted in Example III is a lump of tissue, in view of "preparing specimens of human tissue" "removed from a human colon" and "pathologically diagnosed as colon carcinoma to size by the teasing procedure described earlier." It corresponds to the "neoplastic tissue obtained from a human organ other than brain" of Inventions 1 to 10 and the "neoplastic tissue obtained from a human organ other than brain" of Inventions 11 to 19.

(2) Implantation into a corresponding organ

In "a pocket of cavity" "surgically formed in the seromuscular layer" of the colon of non-human animal model of athymic mouse, inserted is "a tumor mass" "of approximately 0.5 x 0.2 cm" diagnosed as colon carcinoma. As seen above, a colon cancer tissue was implanted in a colon of thymic mouse in Example III. Thus the implantation was made corresponding to "the corresponding organ of said animal" of Inventions 1 to 10.

Further, the implantation corresponding to "the corresponding organ of the immunodeficient animal" of Inventions 11 to 19 was made.

(3) Metastasis

In Example III, it discloses that "Four of the five mice which underwent this implant surgery have survived for three to four months" and "Approximately one month following tissue implantation, the mice were surgically incised and the tumors were observed to have taken." In view of this, one out of five died at any time point; however, the tumors have obviously taken for at least four of the five mice.

Further, one month later, while the mice were surgically opened to confirm the engraftment, an observation was delivered on the metastasis to the other organ as follows: "None of the tumors appeared not to have metastasized to other organs at this time."

This sentence is a double negation, and when summarizing the negation, it is construed as meaning "the tumors appeared to have metastasized to other organ."

Here, you may note an indefinite expression of "appeared"; however, in view of the following description:

(i) The specification describes the matters specifying Inventions 1 to 19 as "non-human animal model for the metastasis of human tumor tissue";

(ii) For background of the Invention, the specification refers to a conventional problem that "In these models, tumors that took often grew to a great extent at the site of implant and rarely metastasized, even if the original tumor had been highly metastatic in the donor. Accordingly, the subcutaneous nude mouse human tumor model, although better than the previously described rodent model, still had a substantial drawback; i.e., the subcutaneous transplant lacked the ability to metastasize."
(the specification, page 3, lines 13 to 17).

(iii) The patent invention solves such a problem, and there is a description that "In accordance with the primary aspect of the present invention, a novel non-human animal model for human neoplastic disease is provided having neoplastic tissue obtained from a human organ implanted into the corresponding organ of the animal and having sufficient immunodeficiency to allow the implanted tissue to grow and metastasize." (The specification, page 3, lines 24 to 26),

it is obvious that it aimed to prepare a non-human animal model with an ability sufficient to metastasize, for which Example III was a confirmatory experiment.

Further, Example III
(iv) was obviously conducted by a person who had a skill in surgery and an ability to confirm the effects of the patent invention, as evident from "Four of the five mice which underwent this implant surgery have survived for three to four months."
(v) The observation of "none of the tumors appeared not to have metastasized to other organs at this time" was made simultaneously with the observation of "Approximately one month following tissue implantation, the mice were surgically opened and the tumors were observed to have taken." Thus it is inferred that the observation was made by sight.
(vi) At least four of the five mice were subjected to a surgical incision one month after the tissue implantation, and the observation was made to the effect that "none of the tumors appeared not to have metastasized to other organs at this time" at the time, as evident from "Four of the five mice which underwent this implant surgery have survived for three to four months."

In view of the description of "none of," evidence that the tumor appeared to have metastasized to other organs was obtained from at least four of five mice; the same evidence was obtained in a plurality of mice.

Further, in view of the description that "Four of the five mice ... have survived for three to four months," it can be seen that any mouse that served for "surgical incision of mouse about one-month after tissue implantation" was sutured, and four of the five mice achieved "survival for three to four months."

As described in the above "(v)," the observation of Example III was made by visual inspection, and a strict inspection such as tissue testing was not conducted, which might lead to the observation such as "appeared"; however, as described in the following Publications A and B, it was a usual practice to confirm the metastasis by visual inspection before the priority date of the Patent. Thus it cannot be said that the observation of Example III was uncertain because it was made by visual inspection. In addition, a person skilled in surgery with an ability to confirm the effects of the patent invention delivered an observation that "None of the tumors appeared not to have metastasized to other organs at this time" which could be seen as a metastasis, in at least four of five mice. In view that it is unusual that the same evidence was observed incidentally and simultaneously in four mice, it is natural to believe that there was a metastasis derived from implanted neoplastic tissue. It cannot be said that the occurrence of metastasis has not been confirmed.

Publication A: Japanese Unexamined Patent Application Publication No. S62-294432
"To a second group of rats injected was a 'void' liposome (i.e. not mixed with MTPChol), whereas a third group of rats was left untreated. Eighteen days after tumor cells implantation, rats of each group were killed, and the number of pulmonary metastases visible to the naked eye was counted." (page 9, the right upper column, lines 4 to 9)

Publication B: Japanese Unexamined Patent Application Publication No. S61-212590

"Effect on the Formation of Metastases of the B16 Melanoma

For the treatment of metastases of the B16 melanoma, a primary tumor was induced in female C57B1/6 mice (10 animals/group) with $2x10^5$ live B16 melanoma cells. After amputation of this tumor the B16 melanoma metastasizes into the lung, and the animals die. After tumor induction, the animals were treated intraperitoneally with 50 mg/kg of the test substance obtained as in Example 7, on any of days 3, 5, 7, 9, 11, and 13 before or after amputation had taken place. The number of macroscopically detectable metastases in the lung was determined on days 14, 17, 21, 25, and 28 after amputation of the primary tumor had taken place.

As is evident from Table 9, the number of pulmonary metastases of the B16 melanoma was markedly less in the treated animal groups than in the corresponding control animals." (page 13, the right bottom column, lines 2 to last line)

3 Allegation from both parties on the basis of the specification as of the International application

Regarding the construction of "None of the tumors appeared not to have metastasized to other organs at this time" of the specification, both parties present an argument on the basis of the description of the specification as of the international application; however, pursuant to the provision of Article 184-4(4) of the Patent Act before revision, of which the provisions then in force shall remain applicable according to revision supplement Article 7 of Heisei 6-nen Law No. 116, the matters that are not described in the translation as of the expiration of Deadline of National Phase Entry but are described in the specification or the scope of claims of International Patent Application as of the International filing date are deemed to be not described in the specification or the scope of claims of International Patent Application as of the International filing date. Therefore, the description of the specification of the International filing date cannot be a ground for the construction of the specification.

4 Judgment by the body

(1) Orthotopic implantation

The means for the use in implementing the Inventions 1 to 19 is orthotopic implantation in view of the description that "The placement of neoplastic tissue in an immunodeficient laboratory animal according to the present invention is carried out by means of orthotopic implantation. This refers to an implant or graft transferred to a position formerly occupied by tissue of the same kind. In the present invention, the terminology orthotopic implantation is used to refer to the grafting of human neoplastic tumor tissue from a human organ into the corresponding organ of an immunodeficient laboratory animal." (The specification, page 4, lines 10 to 13). The specification specifically discloses a method of orthotopic implantation from page 4, line 21 to page 6, line 19, and the specification describes a process of orthotopic implantation for further details in Examples I to III from page 7, line 9 to page 8, line 24.

(2) The fact that targeted technical effects are achievable

A consideration is given as to whether the targeted technical effect might be achieved by the above orthotopic implantation described in the specification. As described in the above "2 Matter to be recognized from Example III," it can be seen from Example III that there was a metastasis derived from an implanted neoplastic

tissue, and thus it is obvious that the targeted technical effects were achieved.

(3) The fact that technical effects are achievable by repeated trials

As discussed in the above "3(3) Metastasis (vi)," a similar evidence like a metastasis was observed in at least four of five mice in Example III of the specification. This suggests that repeated trials brought the same result.

(4) As for Publication distributed after the filing date of the Patent

Evidence B57-1 which is the publication distributed after the filing of the Patent describes a case of direct orthotopic implantation in which a colon cancer specimen was used (Evidence B57-1-3). Although there are several samples that do not cause metastasis (Evidence B57-1-5), in a right side colon infiltrating mucinous adenocarcinoma of sample number 1701, as a result of conducting a direct orthotopic implantation for two mice, one was dead, but the remaining one had a metastasis to the bowel wall (Evidence B57-1-4). Metastasis was confirmed by subjecting the very same neoplastic tissue obtained from the sample to orthotopic implantation.

Evidence B69-1 which is the publication distributed after the filing date of the Patent discloses that, as a result of the orthotopic implantation of a poorly-differentiated giant cell flat epithelium tumor 2268 directly obtained from surgery in the left lung as a histologically intact tissue, the metastasis to the lung of the opposite side has developed together with the metastasis to the lymph node (Evidence B69-1-2). This confirms the metastasis by the orthotopic implantation of the very same tumor tissue obtained from the sample.

Evidence B71-1 which is the publication distributed after the filing date of the Patent obtained a result that six of eight mice (75%) in an orthotopic implantation group had a plurality of metastatic noduli (Evidence B71-1-2) in their lungs by use of a surgical sample (Evidence B71-1-1) of a poorly-differentiated human breast duct cancer (Anticancer#2468). This confirms the metastasis by the orthotopic implantation of the very same tumor tissue obtained from the sample.

Evidence B72-1 which is the publication distributed after the filing date of the Patent obtained a result that tumors of Table 1 (Evidence B72-1-2) were metastasized by use of a duct cancer sample (Evidence B72-1-1) of a fresh chest lining obtained from sidewall chest lining of a 65-year-old white female. It confirms the metastasis by the orthotopic implantation of the very same tumor tissue obtained from the sample.

As seen above, in view of the fact that there are many reports that metastasis was observed by the orthotopic implantation of the very same tumor tissue obtained from the sample, the observation of "None of the tumors appeared not to have metastasized to other organs at this time," which was observed in Example III of the specification, strongly supports the actual metastasis. In addition, it strongly supports the ability to repetitively cause metastasis.

(5) Summary

Comprehensively taking the above matters into account, the means of the aforesaid "orthotopic implantation" of the specification is a means capable of repeated trials that can be easily implemented by a person skilled in surgery, it can be seen from the specification that an evidence like a metastasis was observed in at least four of five

mice prepared by the means, and the metastasis was reproducible, it can be said that Inventions 1 to 19 are configured specifically and objectively to the extent that the technical content can bring about a targeted technical effect through repetitive implementation by a person skilled in the art.

Therefore, it cannot be said that Inventions 1 to 19 were incomplete inventions. Thus the inventions should not be invalidated under the provision of Article 29, main paragraph of the Patent Act.

No. 8 Reasons for Invalidation 2 [Violation of Article 36(3) of the Patent Act (Violation of enablement requirement)]

The objective of Inventions 1 to 19 can be seen from the specification, as mentioned in the above "No. 6 3 The object of Inventions 1 to 19."

Further, the effects of Inventions 1 to 19 can be seen from the specification, as mentioned in the above "No. 6 3 The effects of Inventions 1 to 19."

In addition, the specification describes a means for specifically implementing the constituent elements of Inventions 1 to 19 as set forth below.

1 Neoplastic tissue

The specification specifically describes an access to a "neoplastic tissue obtained from a human organ other than brain" of Inventions 1 to 19 on page 4, line 21 to last line of the specification.

2 Animals with immunodeficiency

An access to "an animal with immunodeficiency" of the Inventions 1 to 19 is described in page 4, lines 3 to 9 of the specification.

3 Orthotopic implantation

The specification specifically describes a means for "implantation into the corresponding organ" (Orthotopic implantation) of Inventions 1 to 19 on page 5, line 1 to page 6, line 19 of the specification.

Furthermore, more specifically, the specification discloses in Example III (the specification, page 8, lines 13 to 24) that the processes of "preparing specimens of human tissue removed from a human colon and pathologically diagnosed as colon carcinoma to size by the teasing procedure described earlier"; "selecting five athymic nude mice, age four (4) to six (6) weeks, as the animal recipients for the implants"; "incising a mouse to provide access to the colon"; "forming a pocket of cavity in the seromuscular layer with care exercised not to enter the lumen"; and "inserting a selected tumor mass of approximately 0.5 x 0.2 cm into the pocket which was then closed with a suture" resulted in "Four of the five mice which underwent this implant surgery have survived for three to four months and appear to be in good health. Approximately one month following tissue implantation, the mice were surgically incised and the tumors were observed to have taken. None of the tumors appeared not to have metastasized to other organs at this time."

4 Summary

Consequently, it can be said that the Detailed Description of the Invention of the

specification describes the objective, the constituent elements and the effects to the extent that allows a person skilled in the art who read the description to implement "an animal model" of Inventions 1 to 10 and "a method of generating an animal model" of Inventions 11 to 19. Therefore, it cannot be said that it does not conform to the requirement under Article 36(3) of the Patent Act before the revision on 1990.

No. 9 Reasons for Invalidation 3 [Article 36(4)(i) of the Patent Act (Violation of supporting requirement)]

The means of the aforesaid "orthotopic implantation" of the specification is a means capable of repeated trials that can be easily implemented by a person skilled in surgery without relation to organs, As described in the above "No. 7 4 Judgment by the body", it can be seen from the specification that metastasis was observed in at least four of five mice, and the metastasis was reproducible.

Therefore, Inventions 1 to 19 are the inventions described in the Detailed Description of the Invention, and it can be recognized from the Detailed Description of the Invention that the problem to be solved by Inventions 1 to 19 described in the above "No. 6 1 Problem to be solved by Inventions 1 to 19" might be solved. Therefore, it cannot be said that the Inventions do not conform to the requirement as provided in Article 36(4)(i) of the Patent Act before the revision in 1990.

No. 10 Reasons for Invalidation 4 [Violation of Article 36(4)(ii) of the Patent Act (Violation of description requirement with regard to constituent elemental function of claim)]

As is discussed in the above "No. 7 2 Matter to be recognized from Example III," it is natural to construe that Example III of the specification showed a metastasis derived from implanted neoplastic tissue. It cannot be said that the occurrence of metastasis has not been confirmed.

Therefore, the demandant's allegation that "it is recognized that the recitation of the scope of claims of the specification which premises the ability of a non-human animal model of the Invention to metastasize does not recite all the indispensable constituent features of the invention for which a patent is sought" is not reasonable. Thus it cannot be said that the scope of claims does not conform to the requirement as provided in Article 36(4)(ii) of the Patent Act.

No. 11 Reasons for invalidation 5 [Novelty or Inventive step]

1 Reasons for invalidation 5-1

(1) The invention described in A1

Generally, in view of (A1-3), (A1-4), and (A1-5) of A1, A1 describes the following invention (hereinafter referred to as "the A1 invention".):

"a nude mouse, wherein the #4 inguinal mammary fat pads of germfree female nude mice 20-25 days of age were cleared of host epithelium by surgical extirpation of the nipple rudiment and adjacent portions of the fat pad up to the site of the inguinal lymph node, and wherein a human breast tissue diagnosed as infiltrating ductal carcinoma is implanted into said cleared portion, and wherein sections of the fat pad 2 months after transplantation showed the tumor to be healthy and beginning to infiltrate the fat pad."

(2) Comparison and judgement

A Inventions 1 to 10

Comparing Inventions 1 to 10 with the A1 invention, they are at least different from each other in that "human breast tissue diagnosed as infiltrating ductal carcinoma" of the A1 invention is the very same tumor tissue sampled from a human organ, and corresponds to "neoplastic tissue obtained from a human organ other than brain" of Inventions 1 to 10,

And, the animal of Inventions 1 to 10 is "a non-human animal model for the metastasis of human neoplastic disease," whereas it cannot be said that the A1 invention is a "non-human animal model for metastasis," because it was a nude mouse with an infiltrating tumor but the metastasis was unknown and it cannot be recognized as an animal model for the use in studies and tests for metastasis in place of the metastasis of human neoplastic disease.

As described in a website of cancer information, PDQR (The body's note: "R" is a character representing R in a circle) Japanese Edition, Cancer terminology dictionary, "infiltrating cancer," [online],
[Search date 2013.01.18], Internet <URL http://cancerinfo.tri-kobe.org/pdq/dictionary/index.jsp>, it describes:
"Infiltrating cancer
[Kana] Shinjun sei gan
[Original text] infiltrating cancer A cancer that spreads beyond the tissue layer originally generated and grows into a surrounding healthy tissue. It is also referred to as 'invasive cancer'." the term "infiltration" means a cancer that is "growing into a surrounding healthy tissue." A cancer that spreads beyond the tissue layer originally generated and grows in a manner that grows into a surrounding healthy tissue.

In contrast, as described on page 98, left column, lines 2 to 5 of B5 that "metastasis means multiple colonies formed by malignant cells separate from an original tumor that sometimes move to a distant site therefrom and spread systemically," it is a different phenomenon different from infiltration.

There was no common general knowledge before the priority date of the application that the infiltration always results in metastasis. Obviously, it cannot be said that the invention described in A1 is "a non-human animal model for the metastasis of human neoplastic disease" of Inventions 1 to 10. Thus it cannot be recognized that the inventions are not patentable under the provision of Article 29(1)(iii) of the Patent Act.

Further, as described in the following "No. 11 3 Reasons for invalidation 5-3" and "No. 11 4 Reasons for invalidation 5-4," A3 and A4 describe ones that were found to metastasize with a tumor tissue that has undergone serial transplantation being an implant.

As aforementioned, in the A1 invention, the use of the very same human breast tissue diagnosed as infiltrating ductal carcinoma" of the A1 invention would not cause metastasis. Therefore, it is obvious that, if a person skilled in the art should read A3 and A4 that causes metastasis with a neoplastic tissue that has undergone serial transplantation, it could not be "a non-human animal model for the metastasis of human neoplastic disease" of Inventions 1 to 10.

Furthermore, it cannot be said that Inventions 1 to 10 were easily conceivable on the basis of the A1 invention in view of the matters described the other respective items of A and the common general knowledge before the priority date according to the Patent.

Therefore, it cannot be said that Inventions 1 to 10 were granted patents in violation of the provision specified in Article 29(2) of the Patent Act.

B Inventions 11 to 19

Comparing Inventions 11 to 19 with the A1 invention, these inventions are at least different from each other in that Inventions 11 to 19 are directed to "a method of generating a non-human animal model for the metastasis of human neoplastic disease," whereas it cannot be said that the A1 invention is a method of generating "a non-human animal model for metastasis," because metastasis is unknown and it cannot be recognized as an animal model for the use in studies and tests for metastasis in place of the metastasis of human neoplastic disease, while a nude mouse with an infiltrating tumor was prepared.

As mentioned in the above "No. 11 1(2)A Inventions 1 to 10," metastasis and infiltration are different phenomena, and there is no common general knowledge before the priority date of the application that infiltration necessarily results in metastasis. Obviously, it cannot be said that the A1 invention is "a method of generating a non-human animal model for the metastasis of human neoplastic disease" of Inventions 11 to 19. Thus it cannot be recognized that the inventions are not patentable under the provision of Article 29(1)(iii) of the Patent Act.

Further, as described in the above "No. 11 1(2)A Inventions 1 to 10," it cannot be said that Inventions 11 to 19 were easily conceivable on the basis of the invention described in A1 in view of the matters described in the other respective items of A and the common general knowledge before the priority date according to the Patent.

Accordingly, it cannot be said that patent Inventions 11 to 19 were granted in violation of the provision specified in Article 29(2) of the Patent Act.

2 Reasons for invalidation 5-2

(1) The invention described in A2

It is recognized from the matters described in (A2-1) of A2 that A2 describes the following invention (hereinafter referred to as "the A2 invention"):

"A nude mouse in which tumors were found within an abdominal wall muscle layer and in a peritoneum in the form of infiltration, adhesion to the peritoneum, the growth within pelvic cavity and gastric wall infiltration, obtained by cutting up subcutaneous passage tumors of fourth passage to sixth passage of a well-differentiated tubular adenocarcinoma of stomach cancer, primary tumors and subcutaneous passage tumors of second passage into a size of 5x5x5 mm, and implanting into an abdominal wall muscle layer, muscle layer-peritoneum, intraperitoneal and gastric wall of a nude mouse (nu/nu--BALB/C/A/BOM, spf) by a surgical procedure."

(2) Comparison and judgement

Comparing Inventions 1 to 10 with the A2 invention, these inventions are at least different from each other in that the animal is an animal model "for the metastasis of human neoplastic disease" in Inventions 1 to 10, whereas it cannot be said that the A2 invention is "a non-human animal model for metastasis," because it was a nude mouse with an infiltrating tumor but the metastasis was unknown and it cannot be recognized as an animal model for the use in studies and tests for metastasis in place of the metastasis of human neoplastic disease.
The A2 invention differs from Inventions 1 to 10 at least in that the metastasis is unknown.

Comparing Inventions 11 to 19 with the A2 invention, they are at least different from each other in description that the method is "a method of generating a non-human animal model for the metastasis of human neoplastic disease" in Inventions 11 to 19, whereas it cannot be said that the A2 invention is a method of generating "a non-human animal model for metastasis," because it cannot be recognized as an animal model for the use in studies and tests for metastasis in place of the metastasis of human neoplastic disease, while a nude mouse with an infiltrating tumor was prepared.

There is no common general knowledge before the priority date of the application that infiltration necessarily results in metastasis. it is obvious that the A2 invention is not "a non-human animal model for the metastasis of human neoplastic disease" of Inventions 1 to 10, nor is it obvious that the A2 invention is "a method of generating a non-human animal model for the metastasis of human neoplastic disease" of Inventions 11 to 19.

Therefore, it cannot be said that Inventions 1 to 19 are identical to the A2 invention, and thus it is impossible to determine that these Inventions are not patentable under the provision of Article 29(1)(iii) of the Patent Act.

Further, for a similar reason to the reasons described in the above "No. 11 1(2)A Inventions 1 to 10" and "No. 11 1(2)B Inventions 11 to 19," it cannot be said that Inventions 11 to 19 were easily conceivable on the basis of the invention described in A2 in view of the matters described in the other respective items of A and the common general knowledge before the priority date according to the Patent, and, it cannot be said that Inventions 11 to 19 were granted patents in violation of the provision specified in Article 29(2) of the Patent Act.

3 Reasons for invalidation 5-3
(1) The invention described in A3

It can be seen from the description of "FIG. 3 Tissue Observation (Hc-4)lung metastatic foci H-E stain" (A3-10) of Evidence A No. 3 that the lung metastatic foci was observed for Hc-4.

Further, this Hc-4 is recognized as being sampled after chemotherapy for cirrhotic liver with hepatoma of a 45-year-old male, in view of the description that
"Three of six cases have taken and become capable of serial transplantation: the samples before and after chemotherapy for cirrhotic liver with hepatoma (Hc-3,4) of a 45-year-old male, differentiated hepatoma (Hc-5) of a 70-year-old male and hepatoblastoma (Hb-1) of a three-year-old male infant, which have been subcultured to sixth passage, second passage, and fourth passage, respectively." (A3-5)

Further, "Remarkably, subcultured second passage rat (The body's note: it is construed as a typographical error of "subcultured second passage mouse" as mentioned in the above "No. 2 3(3) Matters described in A3") formed a tumor mass with a size of about 1.5 cm as a result of the implantation of a piece of tumor mass into a liver at a deep region of a right flank region (FIG. 1). The tumor mass was a massive type, which had spread across the lobes with only a left lateral lobe being left. No ascites fluid or lymph node metastasis to hepatic portal region was observed, but a spherical metastasis with a diameter of about 2 mm was observed in the right lower lobe." It can be seen from the description of (A3-7) that the implanted tumor was a second passage of hepatoma tumor (Hc-4), which was sampled from a 45-year-old male after chemotherapy for a cirrhotic liver with hepatoma, and subcultured in a mouse.

Further, in view of "The mice used were male or female nude mice" (A3-4), the mouse used for implantation was a nude mouse.

Comprehensively taking the above matters into account, it can be recognized that A3 describes the following invention (hereinafter referred to as the "A3 invention"):
"A nude mouse, wherein a second passage of hepatoma (Hc-4) sampled after chemotherapy from cirrhotic liver with hepatoma of a 45-year-old male is implanted into a deep region of a right flank region of the nude mouse, and as a result of implantation of a piece of tissue into a liver, a tumor mass of about 1.5 cm forms and the spherical metastasis with a diameter of about 2 mm is observed in a right lower lobe."

(2) Comparison and judgement

Comparing Inventions 1 to 10 and Inventions 11 to 19 respectively with the A3 invention, these inventions are at least different from each other in that a tumor to be implanted is "a neoplastic tissue obtained from human organ" of Inventions 1 to 10 and "a neoplastic tissue from a human organ" of Inventions 11 to 19, and both of which are, as mentioned in "No. 5 Construction of Inventions 1 to 19," the tumor is "the very same neoplastic tissue itself sampled from a human organ," whereas in the A3 invention, the tumor is "a second passage of hepatoma (Hc-4) sampled after chemotherapy from cirrhotic liver with hepatoma of a 45-year-old male"; i.e., a cultivated neoplastic tissue.

A3 discloses that "Human tumor implanted in a nude mouse showed almost no metastasis. This is supposed to be because of being the animal with immune deficiency, a change of biological nature of implanted tumor, or a death prior to metastasis due to a few case of long-term survival, since it was not conducted under an SPF environment. One possible major factor may be that the implanted site was a hypodermal tissue." Specifically, if implanted in an original organ, it might possibly show a similar metastasis. We would like to believe that the induction of lung metastasis by our liver-implanted hepatocellular tumor had clearly demonstrated this." (A3-12). As aforementioned, "our liver-implanted hepatocellular tumor" is a second passage of hepatoma tumor (Hc-4) that has undergone subcutaneous passage. It only suggests that the implantation of a neoplastic tissue that has undergone subcutaneous passage into an original organ results in a similar metastasis. It does not suggest that the very same neoplastic tissue sampled from a human organ would cause metastasis.

Furthermore, as described respectively in "No. 11 1 Reasons for invalidation 5-1" and "No. 11 2 Reasons for invalidation 5-2," A1 and A2 suggest that the implantation of a tissue that can be seen as the very same neoplastic tissue sampled from a human organ has caused only infiltration. Further, no metastasis was confirmed for the implant of "the very same neoplastic tissue sampled from a human organ" before the priority date according to the Patent.

Therefore, there was no motivation to adopt in the A3 invention "a human breast tissue diagnosed as infiltrating ductal carcinoma" of A1 that only mentions infiltration or "primary tumors" of a "well-differentiated tubular adenocarcinoma of stomach cancer" of A2 in place of "a second passage of hepatoma (Hc-4)," which was a tumor to metastasize that had been subjected to serial cultivation. Therefore, it is difficult even for a person skilled in the art to conceive of Inventions 1 to 10 and Inventions 11 to 19.

4 Reasons for invalidation 5-4

(1) The invention described in A4

A Implanted human hepatoma

A4 discloses that "it was 10 mice which were subjected to the subcostal insertion of a needle into a right flank region of nude mouse to implant into a liver, but it was only two mice consisting of a second passage of Hc-3 and a third passage of Hc-5 that achieved success. Implantation into a liver was conducted by opening the abdominal cavity for two of the sixth passages of Hc-4. Both have taken, but one has gotten wasting disease 18 days after implantation, another 38 days after implantation, and both have died. After death of four, the presence of hepatoma was observed. Further, a lung metastasis was observed in the second passage of Hc-3 implanted into the right subcostal region[27)]." (Evidence A No. 4-9).

According to (A4-5), the "second passage of Hc-3" in which a metastasis to the lung was observed is derived from the one "who got hospitalized in First Surgery Department of Hokkaido University and underwent laparotomy from November 1976 to May 1978" and "the implantation system is described as Hc for hepatocellular tumor, Hb for hepatoblastoma, which are respectively numbered in the order of implantation." Therefore, it can be seen as a second passage of human hepatocellular cancer.

Further, regarding implanted human hepatoma, it discloses that "a piece of tissue of 1 to 2 mm square prepared by the aforesaid method was implanted into a liver middle lobe by use of a needle with an outer diameter of 2.5 to 1.5 mm." (A4-8), "aforesaid method" used herein means that "When tumors that have undergone first passage or serial transplantation reached a certain size, the nude mouse was cardiopunctured under anesthesia with ether, followed by blood drawing, and then tumors were aseptically isolated. This tumor was immediately put into a physiological saline, and cut out into about 2 mm square" (A4-7). Therefore, it can be seen that implanted human hepatoma was obtained by isolating a subcultured human hepatoma from under the skin of nude mouse, and cutting out into a piece of tissue of 1 to 2 mm square.

B Passage

(A4-7) describes "(b) Serial transplantation When tumors that have undergone first passage or serial transplantation reached a certain size, ... (Omitted)... tumors were aseptically isolated. This tumor was immediately put into a physiological saline, and cut out into about 2 mm square, and one or several pieces thereof were

implanted subcutaneously into a lateral region or a dorsal region of another new nude mouse by use of a needle." In view of this, it can be seen that passage means passage by implanting a tumor under the skin of a nude mouse for passage; i.e., subcutaneous passage.

C Mouse in implantation into liver

(A4-8) describes "(c) Implantation into a nude mouse liver." Thus it can be seen as a nude mouse subjected to implantation that is implanted into a liver.

Furthermore, both the nude mouse for implantation and the nude mouse for subcutaneous passage are "male and female BALB/c nude mice (nu/nu) raised under a specific pathogen free condition in Central Institute for Experimental Animals at 5 to 7 weeks old" (A4-4). But as aforementioned, these mice are different in the purpose for implantation and implanting organ. Thus nude mice are distinguished by adding the uses of "for implantation" and "for passage" to nude mice.

D Implantation and metastasis to a liver

It can be seen from the description of (A4-9) that the subcostal insertion of a needle into a right flank region of nude mouse to implant into a liver achieved success only in two of the second passage of Hc-3 and the third passage of Hc-5. Further, it can be seen that "a lung metastasis was observed in the second passage of Hc-3" as a result of "subcostal insertion of a needle into a right flank region of nude mouse to implant into a liver."

Further, in view of "subcostal insertion of a needle into a right flank region of nude mouse to implant into a liver," it is obvious that the implantation was conducted into a liver.

In addition, in (A4-9), "27)" is cited as a document. The document "27)" is "Junichi UCHINO, Takehiko KUWAHARA and others: Implantation into a nude mouse of human hepatoma, Journal of Clinical and Experimental Medicine, 104:31, 1978." (A4-13), which corresponds to A3. As mentioned in the above "No. 11 3(1) The inventions described in A3," the metastasis made a success in "a second passage of hepatoma tumor (Hc-4), which was sampled after chemotherapy from a 45-year-old male bearing a cirrhotic liver with hepatoma, and subcultured in a mouse." On the other hand, it was a "second passage of Hc-3" in A4 that caused a metastasis to the lung. Further, regarding tumors that caused a metastasis to the lung, there is no particular inconsistency between A3 and A4. It is recognized that metastasis to the lung was observed in a second passage of Hc-4 in A3, and a metastasis was observed in a second passage of Hc-3 in A4.

E Infiltration

(A4-12) discloses that "6) Metastasis was observed in only one mouse where an infiltrative tumor was formed in the liver. The mouse was found to have a metastasis to the lung." A4 describes a metastasis to the lung for only the one where "a lung metastasis was observed in the second passage of Hc-3 implanted into a right subcostal region" (A4-9), it can be seen that a metastasis to the lung was observed in "the second passage of Hc-3 implanted into a right subcostal region," and an infiltrative tumor was formed.

F Summary

Comprehensively taking the above matters into account, it can be recognized that A4 describes the following invention (hereinafter referred to as "A4 invention"):
"A nude mouse, in which a metastasis to the lung was observed and an infiltrative tumor was formed, obtained by isolating a second passage tumor of human hepatocellular tumor Hc-3 in which a human hepatocellular tumor Hc-3 has undergone subcutaneous passage in a nude mouse for passage to obtain a piece of tissue with 1 to 2 mm square, and subcostally inserting a needle into a right flank region of a nude mouse for implantation to implant into a liver."

(2) Comparison and judgement

Comparing Inventions 1 to 10 and Inventions 11 to 19 respectively with the A4 invention, these inventions are at least different from each other in that the tumor to be implanted is "a neoplastic tissue obtained from human organ" in Inventions 1 to 10 and "a neoplastic tissue from a human organ" in Inventions 11 to 19, and both of which are, as mentioned in "No. 5 Construction of Inventions 1 to 19," the tumor is "the very same neoplastic tissue itself sampled from a human organ," whereas in the A4 invention, the tumor is "a second passage tumor of human hepatocellular tumor Hc-3 in which a human hepatocellular tumor Hc-3 has undergone subcutaneous passage in a nude mouse for passage"; i.e., a cultivated neoplastic tissue.

On the other hand, as described in "No. 11 1 Reasons for invalidation 5-1" (A1) and "No. 11 2 Reasons for invalidation 5-2" (A2), A1 and A2 suggest that the implantation of a tissue that can be seen as the very same neoplastic tissue sampled from a human organ has caused only an infiltration. Further, no metastasis was confirmed for the implant of "the very same neoplastic tissue sampled from a human organ" before the priority date according to the Patent.

Therefore, there was no motivation to adopt in the A4 invention "a human breast tissue diagnosed as infiltrating ductal carcinoma" of A1 that can be seen as the very same neoplastic tissue sampled from a human organ and only mentions infiltration or "primary tumors" of a "well-differentiated tubular adenocarcinoma of stomach cancer" of A2 in place of ""a second passage tumor of human hepatocellular tumor Hc-3 in which a human hepatocellular tumor Hc-3 has undergone subcutaneous passage in a nude mouse for passage," which was a tumor to metastasize that had been subjected to serial cultivation, Therefore, it is difficult even for a person skilled in the art to conceive of Inventions 1 to 10 and Inventions 11 to 19.

5 Reasons for Invalidation 5-5 to Reasons for Invalidation 5-7

As mentioned in the above "No. 5 Construction of Inventions 1 to 19," it is reasonable to understand that the "neoplastic tissue obtained from a human organ" of Inventions 1 to 10 is the very same neoplastic tissue itself sampled from a human organ. Further, it is reasonable to understand that the "neoplastic tissue from a human organ" of Inventions 11 to 19 is the very same neoplastic tissue itself sampled from a human organ.

Therefore, the auxiliary request of Reasons for Invalidation 5-5 to Reasons for Invalidation 5-7 needs not be considered or determined, since it is based on the premise

that a "neoplastic tissue from a human organ" is construed as including the ones that have undergone subcutaneous passage.

No. 12 Conclusion

As described above, the Patents according to Inventions 1 to 19 may not be invalidated on the basis of the allegation and means of proof presented by the demandant. Further, there is no other reason to invalidate the patents according to Inventions 1 to 19.

The costs in connection with the trial shall be borne by the demandant under the provisions of Article 61 of the Code of Civil Procedure as applied mutatis mutandis to the provision of Article 169(2) of the Patent Act.

Therefore, the trial decision shall be made as described in the Conclusion.

別紙

【書類名】　全文訂正明細書

【発明の名称】　ヒト疾患に対するモデル動物

【特許請求の範囲】

【請求項１】　ヒト腫瘍疾患の転移に対する非ヒトモデル動物であって、前記動物が前記動物の相当する器官中へ移植された脳以外のヒト器官から得られた腫瘍組織塊を有し、前記移植された腫瘍組織を増殖及び転移させるに足る免疫欠損を有するモデル動物。

【請求項２】　動物が無胸腺マウスである、請求項１に記載のモデル動物。

【請求項３】　ヒト腫瘍組織がヒトの肝臓、腎臓、胃、膵臓、結腸、胸部、前立腺、卵又は睾丸から得られる、請求項２に記載のモデル動物。

【請求項４】　腫瘍組織がヒト腎臓から得られる、請求項３に記載のモデル動物。

【請求項５】　ヒト腫瘍腎組織がマウスの腎臓の腎皮質中へ移植される、請求項４に記載のモデル動物。

【請求項６】　腫瘍細胞がヒト胃から得られる、請求項３に記載のモデル動物。

【請求項７】　ヒト腫瘍胃組織がマウスの胃中に、胃の内部粘膜ライニングと胃の外部腹膜コートとの間に移植される、請求項６に記載のモデル動物。

【請求項８】　腫瘍組織がヒト結腸から得られる、請求項３に記載のモデル動物。

【請求項９】　腫瘍結腸組織がマウスの大腸の盲腸中に移植される、請求項８に記載のモデル動物。

【請求項１０】　腫瘍組織が女性ヒト胸部から得られる、請求項３に記載の雌モデル動物。

【請求項１１】　ヒト腫瘍疾患の転移に対する非ヒトモデル動物を作製する方法であって；移植されたヒト腫瘍組織を前記動物中で増殖及び転移させるに足る免疫欠損を有する実験動物を準備し；

脳以外のヒト器官からの腫瘍組織塊の試料を免疫欠損動物の相当する器官中へ移植する、

ことを含む方法。

【請求項１２】　実験動物が無胸腺マウスである、請求項１１に記載の方法。

【請求項１３】　ヒト腫瘍組織がヒトの肝臓、腎臓、胃、膵臓、結腸、胸部、前立腺、肺又は睾丸から得られる、請求項１２に記載の方法。

【請求項１４】　腫瘍組織がヒト腎臓から得られる、請求項１３に記載の方法。

【請求項１５】　ヒト腫瘍腎組織がマウスの腎臓の腎皮質中に移植される、請求項１４に記載の方法。

【請求項１６】　腫瘍細胞がヒト胃から得られる、請求項１３に記載の方法。

【請求項１７】　ヒト腫瘍胃組織がマウスの胃中に、胃の内部粘膜ライニングと胃の外部腹膜コートとの間に移植される、請求項１６に記載の方法。

【請求項１８】　腫瘍組織がヒト結腸から得られる、請求項１３に記載の方法。

【請求項１９】　腫瘍結腸組織が無胸腺マウスの大腸の盲腸中に移植される、請求項１８に記載の方法。

【発明の詳細な説明】

発明の背景

本発明はヒト腫瘍疾患に対する非ヒトモデル動物に関する。より詳しくは、本発明はヒトの器官から得られ、動物の相当する器官中へ移植された腫瘍組織をもつ非ヒトモデル動物に関する。

ヒト腫瘍疾患に代る代表的モデル動物に対する要求が長い間存在した。そのようなモデル動物は多くの目的に役立つことができよう。例えばそれは、ヒトにおける腫瘍疾患の進行を研究して適当な治療形態の発見を援助するために使用できよう。そのようなモデル動物はまた提案された新抗腫瘍物質の効力の試験に使用できよう。さらに、それは癌患者の腫瘍の個別化した化学的敏感性試験に使用できよう。そのようなモデル動物の存在は薬物スクリーニング、試験及び評価を一層効率的にかつ非常に低コストにするであろう。

ヒトの腫瘍疾患に対するモデル動物の作製における若干の以前の試みは移植可能な動物腫瘍を用いた。これらは齧歯動物中に作製し、通常近交集団において、

動物から動物へ移植された腫瘍であった。他の腫瘍モデル動物は少なくとも動物系中で、発癌性であった種々の物質により動物中に腫瘍を誘発させることにより作製された。なお他の腫瘍モデル動物は自然発生腫瘍をもつ齧歯動物であった。しかし、これらの齧歯動物のモデル動物はしばしば、同じ物質を受けるヒト被験者とは非常に異なって化学療法剤に応答した。

約２０年前に始められて開発された他の腫瘍モデル動物は胸腺のないマウスを用いた。これらの動物は細胞に欠陥があり、その結果外来移植組織を拒絶する能力を失なった。該マウスは明確に理解されていない理由のために、実質的に毛がなく、「ヌード」又は「無胸腺」マウスと称されるようになった。

これらのヌードマウスの皮膚の下に皮下的に移植されたときにヒト腫瘍がしばしば増殖することが見いだされた。しかし、そのようなヒト腫瘍組織が実際にマウス中に腫瘍を形成した生着率又は頻度は個々の供与体及び腫瘍の型により変動した。これらのモデル動物において、生着した腫瘍はしばしば、大部分移植の部位で増殖し、もとの腫瘍が供与体中で非常に転移性であってもまれにしか転移しなかった。従って、皮下ヌードマウスのヒト腫瘍モデル動物は、前記齧歯動物のモデル動物よりも良好であるけれども、なお実質的な欠点を有し、すなわち、皮下移植組織は転移する能力を欠いた。

前記不足のないヒト腫瘍疾患のモデル動物に対する要求を満たすために、本発明はヒト中に生ずるような腫瘍疾患の進行に全くよく似た能力を有する新規モデル動物を開示する。

発明の概要及び目的

本発明の主目的はヒト腫瘍疾患に対する改良された非ヒトモデル動物を提供することである。

本発明の主観点によれば、ヒト器官から得られて動物の相当する器官中へ移植された腫瘍組織塊を有し、移植された組織を増殖及び転移させるに足る免疫欠損を有するヒト腫瘍疾患に対する新規非ヒトモデル動物が提供される。

本発明の他の観点はヒト腫瘍疾患に対する非ヒトモデル動物を作製させる方法を提供し、該方法は移植されたヒト腫瘍組織を前記動物中で増殖及び転移させるに足る免疫欠陥を有する実験動物を準備し、ヒト器官からの腫瘍組織塊の試料を

免疫欠損動物の相当する器官中へ移植することを含む。

発明の詳細な説明

本発明のモデル動物は、移植された組織を増殖及び転移させるに足る免疫欠損を有する実験動物中へヒト腫瘍組織塊を移植することにより作製される。この使用に殊に適する実験動物はＴ細胞免疫を有しない系統のマウスである。これらのマウスは、一般にヌードマウス又は無胸腺マウスとして示され、容易に利用でき、チャールス・リバー・ラボラトリーズ〈Charles River Laboratories,Inc.,Wilmington,Massachusetts〉［カタログ確認；Ｃｒｌ；ｎｕ／ｎｕ〈ＣＤ－１〉ＢＲ，同型接合２８～４２日令］から商業的に入手できる。

本発明による免疫欠損実験動物中の腫瘍組織の配置は正位移植により行なわれる。これは、その組織塊が以前に占有していた位置に移植される移植組織塊に関する。本発明において正位移植という語はヒトの器官の新生物腫瘍組織を免疫欠損実験動物の相当する器官中へ移植することを示すために使用される。ここに使用されるヒト腫瘍組織には、例えばヒトの腎臓、肝臓、胃、膵臓、結腸、胸部、前立腺、肺、睾丸及び脳中に生ずる病理学的に診断される腫瘍である外科的に得られた新鮮な試料の組織が含まれる。そのような腫瘍には癌腫並びに肉腫が含まれ、ここに行なわれるそれらの移植はすべての段階、等級及び型の腫瘍を包含する。また、使用されるヒト腫瘍組織は、細胞ごとに分離せず、塊のまま移植する。腫瘍組織を塊のまま移植することにより腫瘍組織が本来もつ三次元的構造が維持されるので、より信頼性の高いヒト腫瘍モデル動物が得られる。

移植の前に、ヒト腫瘍組織は適当な栄養培地，例えば１０％ウシ胎児血清及び適当な抗生物質例えばゲンタマイシンを含むイーグル（Ｅａｇｌｅ）の最少必須培地中に置くことにより維持される。組織を含む培地は次いで約４℃に冷却される。組織はこの方法で約２４時間維持できる。

選択した組織試料は選択した器官中の適当に準備した腔中への挿入に適する大きさの塊に形成することにより移植のために準備される。試料の大きさは約０．１×０．５ｃｍから約０．２×０．６ｃｍまで変動することができる。適当な大きさの試料の形成に使用される技術は鋏子などで所望の大きさの片に引き裂くことにより組織を適当な大きさに引き裂くことが含まれる。

本発明による組織移植の実施に典型的に用いる顕微外科器具にはカストロビジョ（ｃｕｓｔｒｏｖｉｊｅｏ）針ホルダー、ジューアラ（ｊｅｗｅｌｅｒ）の鉗子（直及び曲）、虹彩鉗子、虹彩鋏並びに直及び曲組織鉗子が、各有歯及び各無歯のものを含めて、包含される。

腫瘍組織の移植の前に、選ばれた免疫欠損動物は適当な麻酔薬で麻酔される。肺組織を除いて前記すべての器官組織の移植が、エチルエーテルを用いる普通の麻酔法により便宜に行なわれる。肺組織が移植される場合にはペントバルビタールが麻酔薬として使用される。

ヘパトームからの組織又はヒト肝臓からの腫瘍の移植は移植部位として受容体動物の肝臓の尾状葉を用いて行なわれる。若干のゆるい縫合が葉上に置かれ、大きさ約０．２×０．５ｃｍの腫瘍塊を収容するために縦方向に切開される。切り口中に腫瘍を配置した後、それを適所に確保するために縫合糸を腫瘍上にきちんと引張る。

ヒト膵臓腫瘍からの組織を移植する方法は受容体動物の膵臓中に、十二指腸に近い器官の頭部で切開することにより行なわれる。無血管領域を選ぶことに注意する。切開は選んだ領域中に行なわれ、約０．５×０．２ｃｍの腫瘍塊が前記と同じ方法で移植される。すべての段階及びすべての等級の膵臓癌の組織をこの方法で移植することができよう。

ヒト乳癌からの組織の移植は受容体雌動物の胸上にポケットを外科的に形成することにより行なわれる。ポケットは好ましくは大きさ約０．２×０．５ｃｍの腫瘍塊を収容するに足る大きさである。ポケット中に腫瘍を配置した後、ポケットを縫合で閉じる。すべての段階及び等級の乳癌をこの方法で移植することができよう。

受容体動物の前立腺中へのヒト前立腺癌の組織の移植は、前立腺中に切り口を外科的に形成し、次いで内腔中に大きさ約０．２×０．３ｃｍの組織試料を配置することにより行なわれる。組織試料の配置後、切り口を適当な縫合で閉じる。移植組織が初めの位置から移動できないように２つの追加縫合が前立腺の頸部に置かれる。

受容体動物の睾丸中へのヒト睾丸癌の組織の移植は１８番ゲージ針を睾丸に挿

軸に沿って挿入し、大きさ約０．１×０．５ｃｍの腫瘍塊を針を通して導入することにより行なわれる。組織試料の端が穿刺のときに見えると、針をゆっくり引抜きその間可視腫瘍組織を鉗子で適所に保持する。針により作られた孔は次いで１つの縫合により閉ざされる。

受容体動物の肺中へ腫瘍肺組織を移植する準備中に、気管切開が行なわれ、シラスティック管が挿管される。その後次の移植操作のいずれかを用いることができる；

（１）気管切開管を肺葉（類）に達するまで進め；小細長（２×６ｍｍ）の腫瘍塊を管を通して導入し、次いで管を取出し、気管の創傷を縫合で閉じる；又は

（２）予防管を気管中へ挿入し；右胸上に小穿刺創傷を作り、右肺の葉を引き上げて胸部腔をふさぎ、それにより肺の虚脱を防ぎ；肺葉を基部で弱くクランプして２つの結紮糸を肺の上にゆるく置き；肺上に切り口を作り、約０．２×０．５ｃｍの腫瘍をその中へ埋め、結紮糸をきちんと結び；肺葉を胸部腔中へ戻し、創傷を閉じる。

すべての段階及び等級の小細胞及び非小細胞肺癌の組織を前記操作のいずれかにより移植することができよう。

腫瘍ヒト脳組織を受容体動物脳中へ移植するために、バー孔を動物の頭頂頭蓋骨を通して作る。約０．２×０．４ｃｍの腫瘍塊を選んで脳中へ移植する。次いで頭蓋骨中の孔を骨ロウにより封じる。

本発明のモデル動物はヒト腫瘍疾患の進行の研究において殊に有用である。これらの研究は、他の臨床試験モダリティ例えば診断映像化と組合せて、治療の最も適切な形態の選択に役立つ。

例えば、本発明のモデル動物を腫瘍映像化にかけると、臨床医は腫瘍増殖の一次及び二次両部位を確認し、動物上の腫瘍の全体的な広がりを推定することができる。腫瘍映像化は動物に標識抗腫瘍抗体例えば放射性同位体で標識された抗体を注入し；抗体に腫瘍内で局在する時間を許し；次いで放射線デテクターを用いて動物を走査することにより普通に行なわれる。コンピューターを動物の体中に検出された放射能の映像のコンパイルに使用するときコンピューターは放射線の強度に従って映像をカラーコードすることができる。抗体又はその代謝物質の蓄

積が予想されない体の領域中の高い放射能の帯域は腫瘍の存在の可能性を示す。

本発明のモデル動物はまた新抗腫瘍剤をスクリーニングして一次部位及び遠い転移部位における腫瘍に作用するか又は遠い転移の発生を防ぐそのような物質の能力を決定するために使用できる。該モデル動物はまた癌患者の腫瘍の個別化した化学的敏感性試験に有用であろう。

さらに本発明のモデル動物はヒト腫瘍疾患の進行に対するミトルション（ｍｉｔｒｕｔｉｏｎ）の効果の研究に有用である。これらの研究は健康な被験者に対する種々の欠失の実証衝撃を考えると殊に重要であることができる。

実施例１

ヒト腎臓から切除した腫瘍の組織の外科的に得られた新鮮な試料を５匹の動物受容体の腎臓中へ移植した。腎細胞癌として病理学的に診断された組織試料は前記引き裂き操作により適当な大きさに調製した。

４～６週令の５匹の無胸腺ヌードマウスを移植のための動物受容体として選んだ。外科のための準備中にマウスをエーテルで麻酔した。

各動物中に切開を行ない腎臓に到達した。各受容体腎臓の腎皮質の切除によりくさび状腔を形成し。約０．５×０．２ｃｍの腫瘍組織の塊を欠損腔中に置いた。次いでマットレス縫合を用いて移植組織を適所に確保した。

この実施例の５匹のマウスはその後なお６か月生存している。組織移植の約１か月後にマウスを外科的に切開し、移植腫瘍を観察した。各事例において腫瘍が生着したと認められた。これは移植腫瘍組織が隣接組織に浸潤したことを意味する。このとき、組織学的分析を組織移植片で行なった。そのような分析には各動物から組織試料を取出し、試料を組織供与体の組織試料と比較することが含まれた。

組織学的分析に対する組織試料の調製は、（１）試料をホルマリン中で固定し；（２）固定した試料をパラフィン中に埋め；（３）固定し埋めた試料の５ミクロンの切片を調製し；（４）切片をヘマトキシリン及びエオシンで染色し；（５）各切断面中の組織構造を顕微鏡的に観察することにより行なった。

組織学的分析は、受容体動物中の組織が（１）その構造及び組織型を保持し、（２）ヒト供与体中の疾患の進行によく似ていることを示した。

実施例 II

胃から切除し，胃癌として病理学的に診断されたヒト組織の試料を前記切り裂き操作により適当な大きさに調製した。

４～６週令の５匹の無胸腺ヌードマウスを移植のための動物受容体として選んだ。外科のための準備中にマウスをエーテルで麻酔した。

それぞれの麻酔したマウスを切開して胃に到達した。Ｎｏ．１１小刀を用い，粘膜層に侵入しないように注意して胃壁中に切り口を作った。約０．５×０．２ｃｍの腫瘍塊を受入れるに足る大きさのポケットを形成した。近似的にこの大きさの腫瘍を選び，ポケット中へ挿入し，切り口を７－０縫合糸を用いて閉じた。

この実施例の５匹のマウスは約３～４か月間生存し，他の点では異常がないと思われる。これらのマウスの胃の以後の外科切開は腫瘍が生着したことを証明した。

実施例 III

ヒト結腸から取出され，結腸癌として病理学的に診断されたヒト組織の試料を前記切り裂き操作により適当な大きさに調製した。４～６週令の５匹の無胸腺マウスを移植のための動物受容体として選んだ。外科のための準備中にマウスをエーテルで麻酔した。

それぞれの麻酔したマウスを切開して結腸に到着した。腔のポケットを内腔に入らないように注意して漿膜筋層中に外科的に形成した。約０．５×０．２ｃｍの選んだ腫瘍塊をポケット中へ挿入し，次いでそれを縫合で閉じた。

この移植外科を行なった５匹のマウス中の４匹は３～４か月生存し，良好な健康であると思われる。組織移植の約１か月後にマウスを外科的に切開し，腫瘍が生着したことが観察された。腫瘍はいずれも，このとき他の器官に転移しなかったと思われなかった。

本発明は平明な理解のために例示及び実施例によって若干詳細に記載されたけれども，一定の変更及び改変を請求の範囲内で行なうことができることは明らかであろう。

October 4, 2013

Chief administrative judge: KORIYAMA, Jun
Administrative judge: SAITO, Mayumi
Administrative judge: TAMURA, Akiteru