Date	December 19, 2013	Court	Intellectual Property High Court Second Division
Case number	2012 (Ne) 10054		
– A case in which the court found that it is against the good faith principle to allege constructions that are different from the determination made in the preceding action with respect to a specific constituent feature of the invention in question and thus is impermissible.			

Reference: Article 70, paragraphs (1) and (2) of the Patent Act
Number of related rights, etc.: Patent No. 2664261

Summary of the Judgment

1. The appellant is the patentee of the patent in question (the "Patent"; Patent No. 2664261) for an invention titled "animal model for human disease." The appellant alleges that the nude mouse ("Mouse in This Action") which has been generated by the appellee falls within the technical scope of the invention (the "Invention") pertaining to the patent right in question (the "Patent Right"). Based on this allegation, the appellant seeks payment of damages based on a tort of infringement of the Patent Right. In response to this, in the judgment in prior instance, the court dismissed the appellant's claim by ruling as follows: [i] Based on the good faith principle in the context of litigation, the appellant is not allowed, in this action, to dispute over the literal construction of Constituent Feature [B], for which the determination was made in the preceding action, nor is the appellant allowed to allege infringement under the doctrine of equivalents; and [ii] The Mouse in This Action does not fulfill Constituent Feature [B].

In response to this, the appellant alleges as follows: [a] a civil action is a system to solve specific disputes that have arisen between parties but not a system to set an abstract rule between the parties beyond the purpose first mentioned; and [b] the determination which has been presented in the reasons of the judgment in the preceding action to solve the specific disputes in the preceding action does not bind the civil procedures used to solve this action.

2. In this judgment, the court determined as follows with respect to the aforementioned points and dismissed the appellant's appeal by holding, just for the record, that the Mouse in This Action does not fulfill Constituent Feature [B] and that the fourth requirement is not satisfied with respect to the allegation of infringement under the doctrine of equivalents.

(1) The determination of the technical scope of a patented invention, that is, construction of the constituent features of a patented invention, is a determination of

the fact that is explicitly or implicitly indicated as an essential premise in determining existence or absence of infringement of a patent right. However, this determination also has the nature of a general and abstract rule. Therefore, once it is indicated by the court as a final and binding official determination as the construction of a constituent feature of a patented invention, it serves as the basis for ascertaining the existence or absence of past infringement of the relevant patent right between the parties and has binding force thereon. In addition, such determination also acts as the code of conduct of the parties in the future.

Comprehensively taking into account this point and the aforementioned circumstances that appeared in the evidence in question, in particular, the degree and content of allegations and proof of both parties in the preceding action, the appellant's act of making, against the appellee, an allegation that conflicts with the determinations indicated in the judgments in the preceding action concerning Constituent Feature [B] of the Invention goes against the good faith principle and is impermissible because it harms the appellee's reasonable expectation for legal relations that was formed in a stable manner and forces the appellee to bear the inappropriate burden of counterargument in responding to the action.

(2) In the judgment in the preceding action, the court did not show any determination on the issue of infringement under the doctrine of equivalents. Therefore, there is no circumstance that can serve as a premise among the parties in this regard. In addition, there is no room for the appellee's having a reasonable expectation that the Mouse in This Action is not equivalent to the Invention even if the structure of the mouse in the preceding action and that of the Mouse in This Action are identical with each other because there is originally no final and binding official determination concerning whether or not the mouse in the preceding action is equivalent to the Invention.

Accordingly, it cannot be said that the appellant's alleging infringement under the doctrine of equivalents in relation to the Mouse in This Action goes against the good faith principle in the context of litigation.

Judgment rendered on December 19, 2013
2012 (Ne) 10054 Appeal Case of Seeking Compensation for Damages
(Court of prior instance: Tokyo District Court; 2009 (Wa) 31535)
Date of conclusion of oral argument: October 3, 2013

Judgment

Appellant: Anticancer Incorporated
Appellee: Taiho Pharmaceutical Co., Ltd.

Main text

This appeal shall be dismissed.
The appellant shall bear the costs of the appeal.
The additional period for filing the final appeal against this judgment and a petition for acceptance of final appeal shall be specified as 30 days.

Facts and reasons

No. 1 Objects of the appeal

1. The judgment in prior instance shall be revoked.
2. The appellee shall pay to the appellant 88,000,000 yen and the amount accrued thereon at the rate of 5% per annum for the period from September 17, 2009, to the date of completion of the payment.
3. The appellee shall bear the court costs for both the first and second instances.

No. 2 Outline of the case

1. Summary of the case

(1) Summary of the claim

The appellant is the patentee of the patent in question (the "Patent"; Patent No. 2664261; the application was filed on October 5, 1989; establishment of the Patent was registered on June 20, 1997; the duration expired on October 5, 2009) for an invention titled "animal model for human disease." The appellant alleges that the nude mouse ("Mouse in This Action") which has been generated by the appellee, stated in Description of Mouse attached to the judgment in prior instance, falls within the technical scope of the following invention (the "Invention") claimed in Claim 1 pertaining to the patent right in question (the "Patent Right"). Based on this allegation, the appellant seeks payment of 88,000,000 yen as compensation for damages based on a tort of infringement of the Patent Right (unilateral tort or joint tort with Hamamatsu University School of Medicine) and delay damages.

The Invention is as follows.

[A] A non-human animal model for the metastasis of human neoplastic disease,
[D] which is an animal model that
[B] has a mass of tumor tissue obtained from a human organ other than the brain that was transplanted to the corresponding organ of the aforementioned animal and
[C] exhibits sufficient immunodeficiency to allow the aforementioned transplanted tumor tissue to grow and metastasize.

(2) Decision of the court of prior instance

The court of prior instance ruled as follows: [i] Based on the good faith principle in the context of litigation, the appellant is not allowed, in this action, to dispute over the literal construction of Constituent Feature [B], for which the determination was made in the preceding action (case of seeking injunction against patent infringement between the appellant and the State, the defendant, and other two parties [Tokyo District Court, 1999 (Wa) 15238; Tokyo High Court, 2002 (Ne) 675; Supreme Court, 2003 (O) 197; Supreme Court, 2003 (Ju) 210]), nor is the appellant allowed to allege infringement under the doctrine of equivalents; [ii] The Mouse in This Action does not fulfill Constituent Feature [B] and thus does not fall within the technical scope of the Invention; [iii] The Patent is one that should be invalidated by a trial for patent invalidation because the statement of the scope of claims of the Invention does not comply with the support requirements (Article 36, paragraph (3) of the Patent Act prior to amendment by Act No. 30 of 1990); [iv] Granted that the literal construction of Constituent Feature [B] is as alleged by the appellant, the Invention is one which a person ordinarily skilled in the art could have easily conceived of by applying the knowledge stated in "'Hitokangan no nūdomausukan eno ishoku' (Transplantation of human liver cancer to the liver of a nude mouse), *Igaku no Ayumi*, vol. 104, no. 1 (January 7, 1978): 31 to 33" (Exhibit Otsu 27) to the invention (Exhibit Otsu 14 Invention) stated in"'Hitokangan no nūdo mausu eno ishoku ni kansuru kenkyū: kaishokukei no juritsu to sono seikaku' (Study on the transplantation of human liver cancer to a nude mouse: establishment of a transplantable system and its character), *Kanzō*, vol. 21, no. 3 (1980): 39-51" (Exhibit Otsu 14); therefore, the Patent is one that should be invalidated by a trial for patent invalidation; [v] Granted that the appellant is allowed to allege infringement under the doctrine of equivalents, a person ordinarily skilled in the art could have easily presumptively conceived of the Mouse in This Action by applying the knowledge stated in Exhibit Otsu 27 to Exhibit Otsu 14 Invention; therefore, the Mouse in This Action does not fall within the scope of equivalents of the Invention. Based on these rulings, the court of prior instance dismissed the appellant's claim.

(omitted)

No. 4 Court decision

1. Regarding Issue 1-1 (whether or not filing of this action constitutes a violation of the good faith principle)

This court also determines that it cannot go so far as to recognize the appellant's filing of this action as dredging up the preceding action and as being illegal in violation of the good faith principle in the context of litigation. The reasons therefor are as found and determined from line 9 of page 43 to the end of line 16 of page 51 in the judgment in prior instance. Therefore, the relevant part is cited. However, the phrases "and the judgment in the appeal instance for the preceding action" in lines 16 and 21 of page 45 in the judgment in prior instance are deleted, and "(Issue 1)" in line 14 of page 46 is altered to "(Issue 1-1) and whether or not it is proper to restrict allegations on the grounds of violation of the good faith principle (Issue 1-2)."

The appellee's allegation that goes against the aforementioned finding and determination is unacceptable.

2. Regarding Issue 1-2 (whether or not it is proper to restrict allegations on the grounds of violation of the good faith principle)

(1) Regarding literal construction

According to the part cited from the judgment in prior instance mentioned in 1. above, the following facts are recognized. [i] In the first instance for the preceding action, the main issues were the method of construing the "mass of tumor tissue obtained from a human organ" referred to in Constituent Feature [B] of the Invention and whether or not the mouse in the preceding action fulfills said constituent feature. In the judgment in the first instance for the preceding action, the court ruled that the aforementioned "mass of tumor tissue obtained from a human organ" means a mass of tumor tissue that was taken from a human organ as it is and should be considered as not including a mass of tumor tissue that was taken from a human organ and was successively cultured under the skin of a nude mouse. After that, the court determined that the mouse in the preceding action does not have the aforementioned "mass of tumor tissue obtained from a human organ" and therefore does not fulfill Constituent Feature [B]. [ii] In the appeal instance for the preceding action, the main issues were also the method of construing the "mass of tumor tissue obtained from a human organ" referred to in Constituent Feature [B] of the Invention and whether or not the mouse in the preceding action fulfills said constituent feature. In the judgment in the appeal instance for the preceding action, the court found and determined to the same effect as the judgment in the first instance for the preceding action. [iii] The appellant was dissatisfied with the judgment in the appeal instance for the preceding action, and filed the final appeal and a petition for acceptance of final appeal, but the Supreme Court rendered a ruling that dismissed the final appeal and refused acceptance of the final appeal. [iv] In this action, the appellant made an allegation to the same effect as one in the preceding action, specifically, the "mass of tumor tissue obtained from a human organ" referred to in Constituent Feature [B] should be considered

to include a mass of tumor tissue that was taken from a human organ and was successively cultured under the skin of a nude mouse. [v][1] The Invention does not specify the kind of human tumor tissue, region subject to orthotopic transplantation, size of the piece of tumor tissue to be transplanted, and transplantation method, and the construction of the aforementioned "mass of tumor tissue obtained from a human organ" in the judgment in the first instance for the preceding action and in the judgment in the appeal instance for the preceding action does not change due to differences in these factors. [2] Therefore, although there are differences in structures, such as the kind of the mass of human tumor tissue and the region subject to orthotopic transplantation between the mouse in the preceding action and the Mouse in This Action, [3] the parts where they differ in structures do not affect the construction of the aforementioned "mass of tumor tissue obtained from a human organ" and the conclusion concerning the determination of fulfillment of the constituent feature in the judgment in the first instance for the preceding action and in the judgment in the appeal instance for the preceding action. [vi] There is no circumstance that is sufficient to consider that the appellant did not do its best in advancement of allegations and evidence in alleging and proving that a mass of tumor tissue that was taken from a human organ and was successively cultured under the skin of a nude mouse is included in the "mass of tumor tissue obtained from a human organ" referred to in Constituent Feature [B] in the preceding action. [vii] There is no circumstance that is sufficient to justify the appellant's making an allegation that conflicts with the determinations in the judgements in the preceding action that a mass of tumor tissue that was taken from a human organ and was successively cultured under the skin of a nude mouse is included in the "mass of tumor tissue obtained from a human organ" referred to in Constituent Feature [B]. [viii] There is no circumstance that is sufficient to consider it unreasonable for the appellee to have the expectation that a nude mouse having a structure that is substantially identical with the structure of the mouse in the preceding action does not have the "mass of tumor tissue obtained from a human organ" referred to in Constituent Feature B.

In short, existence or absence of infringement of a patent right is determined based on whether or not the patentee has defined the technical scope of his/her patented invention and whether or not the other party has worked the patented invention in the defined technical scope (see Article 70, paragraphs (1) and (2), Article 68, and Article 2, paragraph (3) of the Patent Act). The determination of the technical scope of a patented invention (excluding the scope of equivalents), that is, construction of the constituent features of a patented invention, is a determination of the fact that is explicitly or implicitly indicated as an essential premise in determining existence or absence of infringement of a patent right. However, this determination also has the nature of a general and abstract rule. Therefore, once it is indicated by the court as a final and binding official determination as the construction of a constituent feature of a patented invention, it, by necessity, serves as the basis for ascertaining the existence or absence of past infringement of the relevant

patent right between the parties and has binding force thereon. In addition, such determination also acts as the code of conduct of the parties in the future. Comprehensively taking into account this point and the aforementioned circumstances that appeared in the evidence in question, in particular, the degree and content of allegations and proof of both parties in the preceding action, it is reasonable to consider that the appellant's making: against the appellee, an allegation that conflicts with the determinations indicated in the judgments in the preceding action concerning the "mass of tumor tissue obtained from a human organ" referred to in Constituent Feature [B] of the Invention goes against the good faith principle and is impermissible because it harms the appellee's reasonable expectation for legal relations that was formed in a stable manner and forces the appellee to bear the inappropriate burden of counterargument in responding to the action. All the appellant's allegations that go against these determination are unacceptable.

In that case, the "mass of tumor tissue obtained from a human organ" referred to in Constituent Feature [B] should be construed as meaning a mass of tumor tissue that was taken from a human organ as it is and not including a mass of tumor tissue that was taken from a human organ and was successively cultured under the skin of a nude mouse, as indicated in the determinations in the judgments in the preceding action.

On the other hand, the Mouse in This Action does not fulfill Constituent Feature [B] because the mass of tumor tissue in the Mouse in This Action is one that was taken from a human organ and was successively cultured under the skin of a nude mouse and is not a mass of tumor tissue that was taken from a human organ as it is.

(2) Regarding the propriety of infringement under the doctrine of equivalents

The appellee alleges that the appellant's allegation that the Mouse in This Action is equivalent to the Invention goes against the good faith principle in the context of litigation and it is thus impermissible.

However, the determinations shown in the judgments in the preceding action are to the effect that the "mass of tumor tissue obtained from a human organ" referred to in Constituent Feature [B] of the Invention means a mass of tumor tissue taken from a human organ as it is and does not include a mass of tumor tissue that was taken from a human organ and was successively cultured under the skin of a nude mouse and that on the premise of this construction, the mouse in the preceding action does not have the "mass of tumor tissue obtained from a human organ" referred to in Constituent Feature [B]. In the judgments in the preceding action, the court did not show any determination concerning whether or not a nude mouse having a mass of tumor tissue that was taken from a human organ and was successively cultured under the skin of a nude mouse is equivalent to the Invention, or whether or not the mouse in the preceding action having a mass of tumor tissue that was taken from a human organ and was successively cultured under the skin of a nude mouse is equivalent to the Invention. Therefore, there is no circumstance that can serve as

a premise among the parties in this regard.

To be sure, whether or not the appellant could allege the doctrine of equivalents in the preceding action can interfere with the appellant's alleging infringement under the doctrine of equivalents in relation to the mouse in the preceding action in the subsequent action, from the perspective of request for a one-time solution of general disputes. However, as the doctrine of equivalents questions whether or not a specific existing subject product is equivalent to a relevant invention, there is no room to discuss the doctrine of equivalents if no subject product exists at the time of making an allegation. Therefore, regarding the Mouse in This Action that is recognized as having not existed at the time of the preceding action (No. 2, 2.(3) above), the appellant could not allege that it was equivalent to the Invention in the preceding action. Therefore, there is no room for request for a one-time solution of the dispute in this case. In addition, for the same reason, the appellant in this action is not prohibited from alleging the doctrine of equivalents in this action just because the appellant, who is the petitioner of the acceptance of the final appeal, alleged, as a reason for the petition for acceptance of final appeal, that the court of the appeal instance for the preceding action did not do its best in the proceedings concerning the application of the doctrine of equivalents, in the appeal instance for the preceding action.

Furthermore, the appellee cites identity between the structure of the mouse in the preceding action and that of the Mouse in This Action as a ground for alleging that the appellant's alleging infringement under the doctrine of equivalents goes against the good faith principle in the context of litigation. However, there is no room for the appellee's having a reasonable expectation that the Mouse in This Action is not equivalent to the Invention even if the structure of the mouse in the preceding action and that of the Mouse in This Action are identical with each other because there is originally no final and binding official determination concerning whether or not the mouse in the preceding action is equivalent to the Invention.

On these bases, it cannot be said that the appellant's alleging infringement under the doctrine of equivalents in relation to the Mouse in This Action goes against the good faith principle in the context of litigation.

Consequently, there is no reason for the aforementioned allegation of the appellee.

3. Regarding Issue 2-1 (whether or not the Mouse in This Action fulfills Constituent Feature [B])

(1) Introduction

Even based on the finding and determination in 2.(1) above, the Mouse in This Action does not fulfill Constituent Feature [B]. However, just in case, a determination is also made concerning Issue 2-1 (whether or not the Mouse in This Action fulfills Constituent Feature [B]).

First, Constituent Feature [B] is stated by the phrase "has a mass of tumor tissue obtained from a human organ other than the brain that was transplanted to the corresponding organ of the aforementioned animal." There is no statement that directly defines the "mass of tumor tissue

obtained from a human organ" in the entirety of the description in question (the "Description"), as well as in the scope of claims. Therefore, there is no other choice but to construe the meaning of the aforementioned "mass of tumor tissue obtained from a human organ" by comprehensively taking into account the individual statements in the Description.

(2) Matters stated in the Description

The following is stated in the Description.

"(lines 8 to 11 of page 12) Background of the invention

The present invention relates to a non-human animal model for human neoplastic disease. More particularly, the present invention relates to a non-human animal model having tumor tissue which was obtained from a human organ and was transplanted to the corresponding organ of the animal model."

"(lines 12 to 18 of page 12) There has long been a need for a representative animal model alternative to human neoplastic disease. Such an animal model could serve many purposes. For example, it could be used to study the progression of neoplastic disease in human subjects and assist in finding appropriate treatment. Such an animal model could also be used to test the efficacy of proposed anti-tumor agents. Additionally, such an animal model could be employed in individualized chemosensitivity testing of a cancer patient's tumors. The existence of such an animal model would make drug screening, testing, and evaluation much more efficient and much less costly."

"(lines 19 to 25 of page 12) Some previous attempts at generating animal models for human neoplastic disease employed transplantable animal tumors. These were tumors that had been generated 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 animals' systems. Still other tumor animal models were rodents containing spontaneously-occurring tumors. These rodent models, however, frequently responded to chemotherapeutic agents very differently from human subjects receiving the same agent."

"(line 26 of page 12 to line 12 of page 13) Mice without a thymus gland were utilized for another tumor animal model that was developed after being started some twenty years ago. These animals were deficient in cells and had 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 being subcutaneously transplanted under the skin of these nude mice. However, the engraftment ratio or frequency with which human tumor tissue actually formed a tumor in the mouse varied depending on the individual donor and the tumor type. In these animal models, engrafted tumors often grew in the regions to which they

were transplanted and rarely metastasized even if the original human tumor had been highly metastatic in the donor. Accordingly, a human tumor animal model of subcutaneous nude mice still had substantial drawbacks, i.e. the subcutaneous transplant tissues lacked the ability to metastasize, though they were better than the aforementioned rodent models.

To meet the need for an animal model for human neoplastic disease without the aforementioned drawbacks, the present invention discloses a novel non-human animal model which has the ability to accurately mimic the progression of neoplastic disease as it occurs in a human subject."

"(lines 13 to 22 of page 13) Outline and purpose of the invention

The main purpose of the present invention is to provide an improved non-human animal model for human neoplastic disease. According to the main aspect of the present invention, the present invention provides a novel non-human animal model for human neoplastic disease having a mass of tumor tissue which was obtained from a human organ and was transplanted to the corresponding organ of the animal and exhibits sufficient immunodeficiency to allow the transplanted tissue to grow and metastasize. In another aspects, the present invention provides a method of generating a non-human animal model for human neoplastic disease, and said method includes a method that comprises preparing a laboratory animal exhibiting sufficient immunodeficiency to allow the transplanted human tissue to grow and metastasize in said animal and transplanting the specimen of a mass of tumor tissue obtained from a human organ to the corresponding organ of the immunodeficient animal."

"(lines 23 to 25 of page 13) Detailed explanation of the invention

The animal model of the present invention is generated by transplanting a mass of human tumor tissue to a laboratory animal exhibiting sufficient immunodeficiency to allow the transplanted tissue to grow and metastasize."

"(lines 3 to 13 of page 14) The placement of tumor tissue in the immunodeficient laboratory animal according to the present invention is carried out by means of orthotopic transplantation. This relates to a mass of transplant tissue that is transplanted in a position that the mass of tissue formally occupied. The terminology "orthotopic transplantation" is used to refer to the transplantation of neoplastic tumor tissue obtained from a human organ to the corresponding organ of an immunodeficient laboratory animal. The human tumor tissue used here includes tissue of fresh surgical specimens which are pathologically diagnosed tumors occurring in, for example, the human kidney, liver, stomach, pancreas, colon, breast, prostate, lung, testis, and brain. Such tumors include carcinomas as well as sarcomas, and transplantation thereof encompasses all stages, grades, and types of tumors. Moreover, the human tumor tissue used is not separated into individual cells but is transplanted as a mass. The transplantation of tumor tissue as a mass leads to maintaining the original three-dimensional architecture of the tumor tissue, which enables

obtaining a more reliable human tumor animal model."

"(line 15 of page 16 to line 4 of page 17) The animal model of the present invention is 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, a clinician can identify both primary and secondary sites of tumor growth and estimate the overall spread of the tumor on the animal. Tumor imaging is conventionally carried out by injecting an animal model 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 model of the present invention can also be used to screen new anti-tumor 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 model will be also useful for individualized chemosensitivity testing of a cancer patient's tumors.

Additionally, the animal model of the present invention is 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."

"(lines 5 to 25 of page 17) Working Example I

Fresh surgical specimens of tissue from a tumor resected from a human kidney were transplanted into the kidneys of five animal recipients. The tissue specimens, which were pathologically diagnosed as renal cell cancer, were prepared to appropriate size by the aforementioned teasing procedure.

Five athymic nude mice aged four to six weeks were selected as animal recipients for the transplantation.

… A wedge shaped cavity was formed by resection of the renal cortex of each recipient kidney and a mass of tumor tissue of approximately 0.5 cm times 0.2 cm was placed within the lost cavity. A mattress suture was then employed to secure the transplantation of tissue in place.

The five mice of this working example are still alive six months later. Approximately one month following the transplantations of tissue, the mice were surgically opened and the transplanted tumors were observed. In each case, the tumor was found to have taken, i.e. the transplanted tumor tissue had invaded adjacent tissue.

Histological analysis revealed that the tissue in the recipient animals [i] preserved its

architecture and tissue type and [ii] mimicked progression of the disease in the human donor.

"(line 26 of page 17 to line 9 of page 18) Working Example II

Specimens of human tissue resected from the stomach and pathologically diagnosed as gastric cancer were prepared to appropriate size by the aforementioned teasing procedure. Five athymic nude mice aged four to six weeks were selected as the animal recipients for the transplantation.

… An incision was made in the stomach wall using a… scalpel, taking care not to penetrate the mucosal layer. A pocket was formed large enough to receive a mass of tumor of about 0.5 cm times 0.2 cm. A mass of 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 working example have survived for about three to four months and otherwise appear healthy. Subsequent surgical opening of the stomach of these mice verified that the tumors have taken."

"(lines 10 to 21 of page 18) Working Example III

Specimens of human tissue removed from a human colon and pathologically diagnosed as colon cancer were prepared to appropriate size by the aforementioned teasing procedure. Five athymic nude mice aged four to six weeks were selected as the animal recipients for the transplantation.

… mouse was opened to provide access to the colon. … a selected mass of tumor of approximately 0.5 cm times 0.2 cm was inserted into the pocket, which was then closed with a suture.

Four of the five mice which underwent this transplantation surgery have survived for three to four months and appear to be in good health. Approximately one month following the tissue transplantation, the mice were surgically opened and the tumors were observed to have taken. All the tumors were not considered to have not metastasized to other organs."

(3) Features of the Invention

The features of the Invention are understood as follows in consideration of the matters stated in the Description as mentioned in (2) above.

Animal models obtained by transplanting a human tumor under the skin of athymic mice which have lost the ability to refuse foreign transplant tissue (nude mice, athymic mice, and athymic nude mice) are better than conventional rodent models. However, the engraftment ratio or frequency with which human tumor tissue actually formed a tumor in the mouse varied depending on the individual donor and the tumor type. In addition, such animal models had a substantial disadvantage, that is, tumors often grew in the regions to which they were transplanted and rarely metastasized even if the original tumor was highly metastatic in the donor, i.e., the human tumor tissue transplanted under the skin lacks the metastatic capacity. Accordingly, there was the problem of generating an animal model for human neoplastic disease which has the ability

to accurately mimic the progression of neoplastic disease in human subjects, that is, an animal model for human neoplastic disease having a human tumor tissue that grows and also metastasizes. Therefore, to solve the aforementioned problem, the present invention has its technical significance in generating a non-human animal model for metastasis having a human tumor tissue which has the ability to accurately mimic the progression of neoplastic disease in human subjects, that is, one which grows and also metastasizes, by adopting a structure wherein a human tumor tissue obtained from a human organ other than the brain is not separated into individual cells but is transplanted as a mass to the corresponding organ of the immunodeficient animal while maintaining the original "three-dimensional architecture" of the tumor tissue (orthotopic transplantation).

(4) Construction of Constituent Feature [B]

A. Consideration of the statements in the Description

The following was revealed through the consideration of the matters stated in the Description as mentioned in (2) above.

[i] The Description states as follows: "(lines 3 to 13 of page 14) …The terminology "orthotopic transplantation" is used to refer to the transplantation of neoplastic tumor tissue obtained from a human organ to the corresponding organ of an immunodeficient laboratory animal. The human tumor tissue used here includes tissue of fresh surgical specimens which are pathologically diagnosed tumors occurring in, for example, the human kidney, liver, stomach, pancreas, colon, breast, prostate, lung, testis, and brain. Such tumors include carcinomas as well as sarcomas, and transplantation thereof encompasses all stages, grades, and types of tumors. Moreover, the human tumor tissue used is not separated into individual cells but is transplanted as a mass. The transplantation of tumor tissue as a mass leads to maintaining the original three-dimensional architecture of the tumor tissue, which enables obtaining a more reliable human tumor animal model."

Therefore, as it is stated that "human tumor tissue used" for the transplantation includes "fresh surgical specimens" obtained from a human organ, said specimens refer to tumors obtained from a human organ as they are. Then, it is stated that said "human tumor tissue used" which was surgically obtained maintains the "original three-dimensional architecture," and the term "original" means that human tumor tissue conventionally has said architecture. In that case, it is obvious that "human tumor tissue" to be transplanted refers to tumor tissue obtained from a human organ as it is.

[ii] Regarding Working Example I, the Description states as follows: "(lines 5 to 25 of page 17) …Fresh surgical specimens of tissue from a tumor resected from a human kidney were transplanted into the kidneys of five animal recipients. The tissue specimens, which were pathologically diagnosed as renal cell cancer, were prepared to appropriate size by the

aforementioned teasing procedure." Regarding Working Example, II, the Description states as follows: "(line 26 of page 17 to line 9 of page 18) … Specimens of human tissue resected from the stomach and pathologically diagnosed as gastric cancer were prepared to appropriate size by the aforementioned teasing procedure." Regarding Working Example III, the Description states as follows: "(lines 10 to 21 of page 18) … Specimens of human tissue removed from a human colon and pathologically diagnosed as colon cancer were prepared to appropriate size by the aforementioned teasing procedure." Tumor tissues taken from human organs were directly transplanted to the corresponding organs of animals.

[iii] On the other hand, there is no statement in the Description suggesting that "human tumor tissue" to be transplanted is specimen that was successively cultured under the skin of a nude mouse.

B. Consideration of the prosecution history

In the written explanation of circumstance concerning accelerated examination (Exhibit Ko 27-1) dated October 31, 1996, which the appellant submitted to the JPO, the appellant alleged as follows: The invention stated in Document (2) ((B)) (1982; translation thereof is Exhibit Ko 27-2) attached to said written explanation wherein two colorectal tumors that have already been established and maintained in a nude mouse are transplanted to the intestinal wall of a nude mouse is a "process of transplanting human intestinal tumor cells to the intestinal wall of an athymic mouse, and therefore, it does not fall under the invention claimed in Claim 1 wherein 'a human tumor cell is transplanted to the organ corresponding to the organ from which the human tumor cell was taken.' In addition, the cell used for the transplantation colonizes or is maintained in the body of the mouse or medium before the transplantation (lines 3 to 4 in the left column of page 331). Therefore, said invention also differs from the invention claimed in Claim 1 in that it does not use a mass of tumor tissue." The appellant then alleged, as a difference between the invention stated in Document (2) above and the Invention, the fact that the animal model of the Invention does not have tumor cells which were successively cultured under the skin of a nude mouse.

It is not necessary to purposely mention successive culture only for the purpose of mentioning a difference between a "tumor cell" and a "mass of tumor tissue." Therefore, the aforementioned statement can be understood as indicating that the appellant itself recognized that the "mass of human tumor tissue" used in the Invention does not include one that was successively cultured under the skin of a nude mouse.

C. Summary

In addition to the aforementioned points, as mentioned in (3) above, taking into account that the Invention is one to solve the problem of providing a non-human animal model for metastasis having metastatic human tumor tissue based on the recognition that human tumor tissue transplanted under the skin has insufficient metastatic capacity or lacks it, it is obvious that the

"mass of tumor tissue obtained from a human organ" referred to in Constituent Feature [B] means a mass of tumor tissue taken from a human organ as it is and does not include a mass of tumor tissue which was obtained by successively culturing a mass of tumor tissue taken from a human organ under the skin of a nude mouse. That is, the Invention should be considered as an invention having as its feature adopting, as a means for solving the aforementioned problem of generating an animal model for human neoplastic disease having metastatic human tumor tissue, the structure wherein a mass of tumor tissue taken from a 'human organ as it is' is directly transplanted to an animal model without successively culturing it under the skin of a nude mouse.

As above, there is no need to further consider other points.

(5) Fulfillment of Constituent Feature [B]

The mass of tumor tissue which the Mouse in This Action has is one obtained by successively culturing tumor tissue taken from a human organ under the skin of a nude mouse and is not a mass of tumor tissue taken from a human organ as it is. Therefore, the Mouse in This Action does not fulfill Constituent Feature [B].

(6) Regarding the allegations of the appellant

A. Regarding the "three-dimensional architecture"

The appellant alleges that the statement of the "three-dimensional architecture" in the Description is nothing more than to make clear that the tissue transplanted to a nude mouse is not tumor tissue.

Although the positive meaning of the "three-dimensional architecture" based on the appellant's construction has not been made clear, in consideration of the appellant's allegation, there is no choice but to reach the understanding that the "three-dimensional architecture" mentioned in the Description is not premised on any specific tissue architecture but means an abstract common architecture that goes across the architecture of a mass of tumor tissue taken from a human organ as it is and the architecture of a mass of tumor tissue which was taken from a human organ and was successively cultured under the skin of a nude mouse. However, it is almost impossible to find such technical idea in the Description. As the natural construction of the statement in the Description, "(lines 3 to 13 of page 14) … the human tumor tissue used is not separated into individual cells but is transplanted as a mass. The transplantation of tumor tissue as a mass leads to maintaining the original three-dimensional architecture of the tumor tissue," it is obvious that the term "tumor tissue" refers to "tissue of fresh surgical specimens" mentioned immediately before it, and it is also obvious that the "original three-dimensional architecture" refers to the architecture of a mass of tumor tissue taken from a human organ as it is. Incidentally, this construction does not carry the connotation that the architecture of a mass of human tumor tissue transplanted to a nude mouse does not change at all even after the transplantation from the objective viewpoint. However, this does not lead to adopting the construction that all of those

tumors whose architecture changed after transplantation also fall within the technical scope of the Invention.

As above, it should be said that the aforementioned allegation of the appellant is unreasonable.

B. Regarding being "fresh"

[i] The appellant alleges that the word "fresh" in the Description is merely to make clear that the specimens are not preserved in a frozen state.

Although the construction of Constituent Feature [B] does not change even based on the aforementioned allegation of the appellant (a mass of human tumor tissue taken from a 'human organ as it is' is also not preserved in a frozen state at the time when it is taken), said allegation can be construed to mean that surgical specimens obtained from a human organ as stated in the Description and transplanted specimens as stated in the Description differ from each other, and that successive culture can be carried out between them.

However, it is stated in Working Example I in the Description that "fresh surgical specimens" from a human organ are directly "transplanted" (lines 6 to 7 of page 17), and fresh specimens to be transplanted are those surgically obtained from a human organ. Therefore, the aforementioned construction cannot be adopted.

[ii] In addition, the appellant alleges that the "human tumor tissue" of the Invention includes those specimens other than tumor tissue taken from a human organ, based on the grounds that there is the following statement in the Description: "(lines 6 to 9 of page 14) The human tumor tissue used here includes tissue of fresh surgical specimens which are pathologically diagnosed tumors occurring in, for example, the human kidney, liver, stomach, pancreas, colon, breast, prostate, lung, testis, and brain."

However, the word "includes" in the aforementioned part is nothing more than to simply clearly specify that those indicated as examples in the aforementioned part can be the elements of the "tissue of fresh specimens," and it can hardly be considered as suggesting existence of any other elements.

[iii] On these bases, all the aforementioned allegations of the appellant are unreasonable.

C. Regarding response to the efficacy evaluation test

The appellant alleges as follows: The Description states that the animal model of the Invention can be used for the efficacy evaluation test of anti-tumor agents; for that purpose, it is necessary to secure the sufficient amount of tumor tissue by using successive culture under the skin of a nude mouse, and therefore, tumor tissue which was taken from a human organ and was successively cultured under the skin of a nude mouse is also included in a "mass of tumor tissue obtained from a human organ."

However, the aforementioned part corresponds to the following statement in the "Background of the invention" section in the Description: "(lines 12 to 18 of page 12) There has long been a

need for a representative animal model alternative for human neoplastic disease. Such an animal model could serve many purposes. For example, it could be used to study the progression of neoplastic disease in human subjects and assist in finding appropriate treatment. Such an animal model could also be used to test the efficacy of proposed anti-tumor agents. Additionally, such an animal model could be employed in individualized chemosensitivity testing of a cancer patient's tumors. The existence of such an animal model would make drug screening, testing, and evaluation much more efficient and much less costly." The statement to the effect that such an animal model can be used to test the efficacy of a new anti-tumor agent is one that is related to a generally needed animal model as stated by the phrase "such an animal model" in the aforementioned part, and is not related to the specific utility of the animal model pertaining to the Invention. The Description also emphasizes the usefulness of the animal model pertaining to the Invention in relation to individual patients or test subjects (line 15 of page 16 to line 4 of page 17), and the usefulness of the Invention does not affect the objective construction of Constituent Feature [B] as mentioned in (4) above.

Therefore, the aforementioned allegation of the appellant lacks its premise and is thus unreasonable.

D. Regarding the prosecution history

The appellant alleges that it was premised in the procedure of the opposition to the granted patent in question (the "Procedure of the Opposition to the Granted Patent") that a "mass of tumor tissue obtained from a human organ" includes a mass of tumor tissue which was taken from a human organ and was successively cultured under the skin of a nude mouse. However, it is not the case that matters which the parties did not dispute but considered as premises in said procedure are objectively legitimate facts. Therefore, the findings and determinations in this action are not immediately affected by the matters that were considered as premises in the course of said procedure.

Incidentally, the experiment stated in the written petition (Exhibit Ko 29) submitted by the appellant in the Procedure of the Opposition to the Granted Patent is recognized as having been conducted after the priority date of the application in question (the "Application") (Exhibits Ko 9-2 [1991; translation thereof is Exhibit Ko 9-2-2], 29, and 35 [1991; translation thereof is Exhibit Ko 35-2-2]), and even if a mass of tumor tissue which was taken from a human organ and was successively cultured under the skin of a nude mouse is used in said experiment, such fact does not affect the construction of the scope of claims of the Invention.

Therefore, the aforementioned allegation of the appellant is unreasonable.

E. Regarding common general technical knowledge

It is hard to understand the appellant's allegation in this regard, and the appellant seems to mix allegations that differ in effect. However, it can be tentatively organized as follows.

[i] The appellant first alleges that successive culture was well-known and commonly-used art as of the priority date of the Application.

However, a mass of tumor tissue which was taken from a human organ and was successively cultured under the skin of a nude mouse is naturally incorporated in the technical scope of the Invention just because a method, successive culture, is well-known and commonly-used art. Therefore, the appellant's allegation to this effect is unreasonable.

[ii] Next, the appellant alleges as follows: [1] As of the priority date of the Application, it was common general technical knowledge that human tumor tissue which was successively cultured under the skin of a nude mouse maintains the histological feature of the human tumor tissue; [2] It was common general technical knowledge among persons ordinarily skilled in the art that, even in a mouse to which tumor tissue directly taken from a human organ was first transplanted, interstitial tissue in a mass of tumor tissue is not of human origin but is replaced with interstitial tissue originating from a nude mouse.

[1] However, even if histological feature is maintained even after successive culture, this does not leads a mass of tumor tissue which was taken from a human organ and was successively cultured under the skin of a nude mouse to be naturally incorporated in the technical scope of the Invention. In order to determine the technical scope of a patented invention, it is necessary to allege and prove what feature was specifically understood by persons ordinarily skilled in the art as being maintained. In the case of the Invention, it is necessary that there was established common general technical knowledge that a mass of tumor tissue which was taken from a human organ as it is and a mass of tumor tissue which was taken from a human organ and was successively cultured under the skin of a nude mouse are equivalent to each other in terms of the metastatic capacity, which is the feature of the Invention. However, as mentioned in [iv] later, there is no sufficient evidence to recognize this point.

[2] Moreover, there is also no sufficient evidence to recognize that it was common general technical knowledge as of the priority date of the Application that, even in a mouse to which a mass of tumor tissue taken from a human organ was first transplanted, interstitial tissue in a mass of tumor tissue is not of human origin but is replaced with interstitial tissue originating from a nude mouse, and that said mass of tumor tissue is equivalent to a mass of tumor tissue which was taken from a human organ and was successively cultured under the skin of a nude mouse (experiment of Exhibit Ko 8 is based on art after the filing of the Application, and it only makes clear that the interstitial tissue of the nude mouse from which a mass of tumor tissue was taken is replaced with that of a nude mouse to which the mass of tumor tissue is transplanted).

Therefore, all the aforementioned allegations of the appellant are unreasonable.

[iii] Furthermore, the appellant alleges that existence or absence of successive culture under the skin originally has no relationship to metastasis because it was publicly-known scientific fact

as of the priority date of the Application that human tumor tissue transplanted under the skin of a nude mouse lacks the metastatic capacity.

However, as instructed in (3) above, the Invention is one related to the problem of providing a non-human animal model having metastatic human tumor tissue with sufficient metastatic capacity under the recognition that human tumor tissue transplanted under the skin has insufficient metastatic capacity or lacks it. Therefore, the existence or absence of successive culture under the skin is significantly related to the structure of the Invention.

Consequently, the aforementioned allegation of the appellant is unreasonable.

[iv] The appellant then alleges that it was common general technical knowledge as of the priority date of the Application that the metastatic capacity of human tumor tissue is not lost even if human tumor tissue is successively cultured under the skin of a nude mouse.

However, the phrase "a mass of tumor tissue obtained from a human organ" can be considered as including "a mass of tumor tissue which was taken from a human organ and was successively cultured under the skin of a nude mouse" in consideration of common general technical knowledge only in the case where persons ordinarily skilled in the art had knowledge that "a mass of tumor tissue obtained from a human organ" and "a mass of tumor tissue obtained by successively culturing a mass of tumor tissue taken from a human organ under the skin of a nude mouse" are identical with each other in metastatic capacity as of the priority date of the Patent Right, and not in the case where persons ordinarily skilled in the art just had knowledge that a human tumor cell does not lose its metastatic capacity even if it is successively cultured under the skin of a nude mouse. In addition, looking at each document, [1] Document (3) attached to Exhibit Ko 27-1 (1981; translation thereof is Exhibit Ko 27-3), Exhibit Ko 47-1 (1978; translation thereof is Exhibit Ko 47-2), Exhibit Ko 50-1 (1975; translation thereof is Exhibit Ko 50-2 and 3), Exhibit Ko 51-1 (1978; translation thereof is Exhibit Ko 51-2 and 3), Exhibit Ko 52-1 (1980; translation thereof is Exhibit Ko 52-2), Exhibit Ko 53-1 (1984; translation thereof is Exhibit 53-2 and 3), Exhibit Ko 54-1 (1984; translation thereof is Exhibit 54-2), and Exhibit Ko 56-1 (1985; translation thereof is Exhibit Ko 56-2) do not refer to the relationship between successive culture and metastatic capacity. [2] Exhibit Ko 2 attached to Exhibit Ko 28-1 (1986; translation thereof is Exhibit Ko 28-3-2) states that it has been proven to a sufficient extent that a human tumor transplanted under the skin or in the muscle of a nude mouse rarely metastasizes. [3] In Exhibit Ko 5 attached to Exhibit Ko 28-1 (1988; translation thereof is Exhibit Ko 28-6), a tumor cell line that was injected under the skin of a nude mouse is not recognized as being selected as a highly-metastatic cell line and provided for an experiment concerning metastasis. [4] Exhibit Ko 104-1 (1988; translation thereof is Exhibit Ko 104-2-1; same as Material 3 attached to Exhibit Otsu 6) does not state that a tumor cell that was successively cultured under the skin of a nude mouse was provided for an experiment concerning metastasis. [5] Regarding metastatic capacity, Exhibit Ko

74 (1982) states that metastasis is comparatively little in the case of transplantation under the skin and that there is no metastasis after repeated successive culture. [6] Exhibit Otsu 15 (1986) refers to metastasis but states that it is necessary to select a tumor line as a metastatic model. Therefore, it is premised that a human tumor which was transplanted under the skin of a nude mouse does not necessarily maintain the metastatic capacity. Therefore, it cannot go so far as to recognize that there was common general technical knowledge that the metastatic capacity of a human tumor cell is not lost even after successive culture under the skin of a nude mouse, as of the priority date of the Application.

However, Exhibit Ko 114-1 (1986; translation thereof is Exhibit Ko 114-2-1) states that a tumor line which was transplanted under the skin of a nude mouse and was established through repeated successive culture was used to study the metastasizing behavior. Exhibit Ko 115-1 (1986; translations thereof are Exhibits Ko 115-2-1 and 115-3; same as Document (1) attached to Exhibit Ko 27-1, Exhibit Ko 3 attached to Exhibit Ko 28-1, and Material 2 attached to Exhibit Otsu 6) are intended to study the growth and occurrence of metastasis of tumor cell lines obtained under five different separation conditions, and one of those conditions is recognized as going through successive culture under the skin (going through growth under the skin of a nude mouse only once). However, these documents alone only indicate that there were publicly known documents concerning experiment results suggesting that the metastatic capacity of a human tumor cell is not lost even after successive culture under the skin of a nude mouse, and it can hardly be said that there was established common general technical knowledge that the metastatic capacity of a human tumor cell is not lost even after successive culture under the skin of a nude mouse. Incidentally, the appellant alleges that there is the statement that "… was consistent with the past reports (11, 13, 15, and 30) that continuous successive culture of a human tumor in a nude mouse does not affect the possibility of metastasis …" in Exhibit Ko 114-1. However, Exhibit Ko 114 only states "… was consistent with the past reports (11, 13, 15, and 30) that continuous successive culture of a human tumor in a nude mouse does not significantly increase the possibility of metastasis …."

The appellant submitted no other material that is sufficient to indicate that there was common general technical knowledge that the metastatic capacity of a human tumor cell is not lost even after successive culture under the skin of a nude mouse, as of the priority date of the Application.

On these bases, the aforementioned allegation of the appellant is unacceptable.

(7) Summary

Therefore, literal infringement is not established in relation to the Mouse in This Action.

4. Regarding Issue 2-2 (whether or not the Mouse in This Action is equivalent to the Invention)

(1) Regarding non-fulfillment of the fourth requirement

A. Mouse in This Action

The Mouse in This Action is as follows, as stated in Description of Mouse attached to the judgment in prior instance.

"(A) A non-human animal model which was made for the purpose of animal evaluation experiment on the blocking effect, etc. on bowel cancer metastasis exerted by a new anti-tumor agent, TSU68, for which the defendant is carrying out a test for applying for permission of manufacturing and sale thereof, (F) which is an animal model (E) made through orthotopic transplantation by sewing, with a 6-0 Polysorb suture (made by Tyco Healthcare), to the cecal wall of (D) a male nude mouse aged six weeks (BALB/c nu/nu: Clea Japan, Inc.), (B) tumor tissue of human bowel cancer line TK-4, which is obtained from human bowel cancer and has high metastatic property that has been maintained by a method of successive culture under the skin (however, this was established in 1993 from the pathological lesion in the involved liver of a Japanese male aged 50 who was affected by sigmoid colon cancer at Second Department of Surgery, Hamamatsu University School of Medicine), (C) as a 120mg piece (mass) of tumor."

B. Matters stated in Exhibit Otsu 14

The following is stated in Exhibit Otsu 14 ("Hitokangan no nūdo mausu eno ishoku ni kansuru kenkyū: kaishokukei no juritsu to sono seikaku" (Study on the transplantation of human liver cancer to a nude mouse: establishment of a transplantable system and its character), *Kanzō*, vol. 21, no. 3 (March 25, 1980): 39-51) (the cited parts are specified as in the original article).

"(lines 2 to 11 in the left column of page 39) Methods based on cell culture or animal transplantation are used for the studies of the biological characteristics of human cancer and various anticancer studies. However, these methods are not necessarily possible depending on the type of tumor. … In particular, an animal affected by human cancer is an ideal model for studying biological characteristics of and various therapeutic effects on the tumor, but it is a required condition that the original character of transplanted human cancer does not change due to the host animal."

"(line 20 in the left column of page 39 to line 2 of the right column thereof) On the other hand, studies of human liver cancer have been conducted through clinical approach and by using liver cancer developed in animals because it is difficult to establish a cultivated cell line thereof."

"(lines 3 to 8 in the right column of page 39) From such perspective, the author attempted to successively culture human liver cancer by transplanting it to a nude mouse. As a result, the author could establish one successive transplantation system. Therefore, the author reports knowledge which was obtained by considering said system, as well as 14 other examples wherein the author could not establish a system through successive transplantation, with regard to the biological characteristics of human liver cancer transplanted to a nude mouse and the propriety thereof as the subject of human liver cancer studies."

"(lines 10 to 13 in the right column of page 39) 1. Experimental animals

Male and female BALB/c nude mice (nu/nu) aged five to seven weeks which were bred under specific pathogen free conditions at the Central Institute for Experimental Animals were used."

"(line 19 in the right column of page 39 to line 2 of page 40) 2. Experimental method

Sixteen liver cancer patients were admitted into the Department of First Surgery of Hokkaido University Hospital from November 1976 to May 1978 and underwent abdominal surgeries. In 14 of these examples, 15 pieces of liver tumor tissue, which can be transplanted to nude mice, could be taken during surgery or from resected specimens. These pieces of tissue were subjected to primary transplantation to nude mice, and those that took were further successively transplanted."

"(lines 8 to 9 of page 40) Incidentally, for the transplantation system, liver cell cancer is described as Hc, and hepatoblastoma is described as Hb. They were numbered in the order of transplantation."

"(lines 11 to 17 in the left column of page 40) (a) Primary transplantation

Liver tumor tissue was aseptically taken by partial resection of tumor or from resected specimens of liver … is shredded into less than 2 mm squares after removing the necrotic zones and blood components. Then, one or a few pieces of tissue were transplanted under the skin of the flank or dorsal region of a nude mouse with a transplantation needle."

"(lines 23 to 33 in the left column of page 40) (b) Successive transplantation

When a tumor that was subjected to primary or successive transplantation reached a certain size, the nude mouse was subjected to cardiopuncture under ether anesthesia, and the tumor was aseptically extracted after blood drawing. This tumor was immediately put in physiological saline water, and was shred into approximately 2 mm squares. One or a few shredded pieces were transplanted under the skin of the flank or dorsal region of another nude mouse with a transplantation needle. … These successive transplantations were carried out after the diameter of the tumor exceeded approximately 1 cm, a point when the tumor rarely bleeds, undergoes central necrosis, and develops an ulcer."

"(lines 34 to 39 in the left column of page 40) (c) Transplantation to the liver of a nude mouse

A nude mouse was subjected to laparotomy under ether anesthesia, and a 1 to 2 mm square piece of tissue generated by the aforementioned method was transplanted to the middle lobe of the liver with a transplantation needle whose external diameter is 2.5 mm to 1.5 mm. In addition, this transplantation was carried out by inserting the transplantation needle under the costal arch of the right flank region of the nude mouse so that the piece of tumor tissue contacts the lateral segment of the right lobe of the liver."

"(lines 13 to 16 in the right column of page 40) 3) Macroscopic findings

Mice which died after the removal of a tumor for successive transplantation or due to any other cause were subjected to autopsy, and the behavior of the tumor and existence of distant

metastasis were observed by the naked eye."

"(line 6 in the right column of page 41 to line 23 of page 42) 1. Biological characteristics of transplanted tumor and record of primary transplantation

… Transplantation to the liver by inserting a transplantation needle under the costal arch of the right flank region was carried out for 10 mice, but it succeeded only in two mice, specifically, the second generation of Hc-3 and the third generation of Hc-5. Transplantation to the liver by laparotomy was carried out for two mice with the sixth generation of Hc-4. The transplanted tumor took in both of those mice, however, … slaughtered. For all of those four mice, existence of a liver tumor was confirmed after slaughter. In addition, lung metastasis of the second generation of Hc-3, which was transplanted under the right costal arch, was recognized.[27)]"

"(right column of page 49) Documents

…

27) Uchino Junichi, Kuwahara Takehiko, et al., "Hitokangan no nūdomausukan eno ishoku" (Transplantation of human liver cancer to the liver of a nude mouse), *Igaku no Ayumi*, vol. 104 (1978): 31."

The aforementioned document "27)" is Exhibit Otsu 27.

"(line 24 in the left column of page 42 to line 2 in the right column of page 42) 2. Successive transplantation

Six examples for which primary transplantation succeeded were subjected to successive culture, and for all the examples, second-generation transplantation also succeeded. Furthermore, successive transplantation was continued."

"(lines 26 to 31 in the left column of page 48) In addition, it is very interesting that the AFP value was more than 10 times higher for mice in which a tumor was directly transplanted to the liver than other mice. The site of tumor origin and the AFP value are issues to be considered in the future. It is expected that there is some sort of difference between transplantation of liver cancer under the skin and to the liver in terms of the engraftment ratio and biological characteristics of the transplanted tumor."

"(lines 3 to 18 in the right column of page 48) V. Conclusion

As a result of successive transplantation of 15 masses of tumor tissue taken from 14 patients to nude mice, the following conclusion was obtained. 1) The primary transplantation succeeded in five out of 13 liver cell cancer cases as well as one of two hepatoblastoma cases. … 4) AFP was detected in all of the six cases in which the tumor took. 5) The transplanted liver cell cancer showed appearance similar to that of the original tumor though its cell nest formation was not prominent. 6) Metastasis was seen in only one mouse wherein an invasive tumor was formed in the liver, and it was to the lung. 7) The metastasis was identified as being of human origin by karyotype analysis, serum absorption test, precipitation reaction by anti-human AFP serum, etc."

C. Matters stated in Exhibit Otsu 27

The following is stated in Exhibit Otsu 27 ("Hitokangan no nūdomausukan eno ishoku" (Transplantation of human liver cancer to the liver of a nude mouse), *Igaku no Ayumi*, vol. 104, no. 1 (January 7, 1978): 31 to 33."

"(lines 1 to 5 in the left column of page 31) An animal affected by human cancer is an ideal model for studying the biological characteristics of the tumor and various therapeutic effects, but it is a required condition that the original character of transplanted human cancer does not change in the host animal, and it is desired that it develops into the original organ."

"(lines 9 to 15 in the left column of page 31) Since then, various types of human cancer have been transplanted to nude mice, and one of the authors succeeded in the transplantation of pancreas cancer.[2)] However, all of these transplantations were carried out to the subcutaneous tissue.

We have mainly attempted to transplant liver cancer to nude mice since 1976. We recently succeeded in the transplantation of human liver cancer to the liver of a nude mouse for the first time, so we are reporting it."

"(lines 16 to 28 in the left column of page 31) Experiment method

Out of eight liver cancer cases for which we performed operations during the period from October 1976 to July 1977, pieces of liver cancer tissue obtained in three cases involving resection and four cases involving only test resection were transplanted. The used mice are male or female nude mice, and their genetic background is BALB/C. They were provided by the Central Institute for Experimental Animals. …

Regarding the transplantation method, liver cancer tissue taken by resection or with a needle was made into a 2 mm square piece of tissue in physiological saline water, and was transplanted under the skin of the abdominal or dorsal regions on both sides (near the lateral segment of the liver on the right side) with a transplantation needle."

"(line 31 in the left column of page 31 to line 3 in the right column of the same page) Experiment result

The number of pieces of liver cancer tissue transplanted so far is seven which were obtained from six cases, specifically, one hepatoblastoma case and five liver cell cancer cases. Out of these, in three cases, the tissue took and became available for successive transplantation. Specifically, these cases are for pieces of tissue taken from the indurated complicated liver cancer of a male aged 45 before and after chemotherapy (Hc-3,4), from the differentiated liver cancer of a male aged 70 (Hc-5), and from the hepatoblastoma of a boy aged 3 (Hb-1), and they are in the course of the sixth/second/and fourth-generation successive transplantation, respectively."

"(lines 11 to 14 in the right column of page 31) The AFP value was 8.2 μg/ml for Hc-4 in the patient serum. However, by the SRIA method, some rats that received transplantation were

positive while others were negative. For positive rats, AFP was detected only in those with the second and third generations of Hb-4, and the AFP value was 10.1 μg/ml and 9μg/ml, respectively."

Incidentally, the term "rats" mentioned above is recognized as an erroneous description of "nude mice."

"(line 18 in the right column of page 31 to line 7 in the right column of page 32) What should be specially noted is that an approximately 1.5 cm tumor mass was formed in the rat that underwent second successive culture as a result of transplantation of a piece of tumor, which was transplanted to the deep part of the right flank region, to the liver (Figure 1). The tumor mass was in the massive form and was covering the entire lobe, except only the left lateral lobe. Neither ascites fluid nor lymph node metastasis in the hepatic portal region was recognized, but a ball-like metastasis of approximately 2 mm in diameter was recognized in the lower lobe of the right lung.

According to histological findings, the fibrous capsule around the tumor was thin and partially hemorrhagic and involved many mitoses for those developed in the liver, unlike those developed in the subcutaneous tissue (Figure 2).

Fiber cells are only in one layer of the capsule of the lung metastasis, and there is almost no reactive change in the surrounding lung tissue. The central part had fallen into necrosis (Figure 3)."

Incidentally, the term "rat" mentioned above is recognized as an erroneous description of "nude mouse."

"(explanation of Figure 1 in page 31) Figure 1 Liver of a nude mouse to which human liver cell cancer was transplanted (divided face)
Being partially hemorrhagic and in the massive form, covering the entire lobe except the left lateral lobe"

"(explanation of Figure 2 in page 32) Figure 2 Histological findings (Hc-4)
(A) Liver tumor before transplantation (B) Tumor developed in the liver of a nude mouse H-E dyeing"

"(explanation of Figure 3 in page 32) Figure 3 Histological findings (Hc-4)
Lung metastasis H-E dyeing"

"(line 26 in the right column of page 32 to line 10 in the left column of page 33) In the past, transplantation sites were under the skin of the dorsal region, lower limb, etc. However, this may make the reaction mode of tissue surrounding a tumor be different from that of the original organ. That is, human liver cell cancer that developed under the skin ordinarily presents a ball-like shape and is covered with relatively thick fibrous capsule. However, in our liver transplantation examples, human liver cell cancer formed almost no fibrous capsule and is partially hemorrhagic,

and it slightly differs from one that developed under the skin in some aspects. In addition, it was accompanied by lung metastasis.

Most have reported that no metastasis was recognized in the transplantation of human cancer to a nude mouse,[5)-8)] and only A reported metastasis.[9)] A microscopic metastatic focus was discovered in the regional lymph node in the case of liver cell cancer of the second-generation. However, there is no report of lung metastasis."

"(lines 11 to 19 in the left column of page 33) The possible reasons for almost no metastasis of human cancer that was transplanted to nude mice are that nude mice are immune-deprived animals, that the biological characteristics of the transplanted tumor changed, or that only few such nude mice survived for a long period of time because of not being in the SPF environment, and such nude mice died before occurrence of metastasis. However, transplantations being carried out to subcutaneous tissue can also be one of the key factors. That is, there is the possibility that a tumor will present similar metastasis if it is transplanted to the original organ. We would like to think that the fact that our liver cell cancer transplanted to the liver caused lung metastasis had clearly proven such possibility."

"(lines 1 to 4 in the right column of page 33) Summary

We reported our success in the transplantation of human liver cancer to the liver of a nude mouse. The tumor transplanted to the liver was slightly different from one transplanted under the skin in terms of the mode of development, and it had no tumor fibrous capsule and had caused lung metastasis."

D. Finding of the gist of Exhibit Otsu 14 Invention

Comprehensively considering the statements in B. above, Exhibit Otsu 14 Invention is recognized as follows.

"A nude mouse wherein an invasive tumor was formed and lung metastasis was recognized, which was obtained by extracting a tumor of the second generation of human liver cell cancer Hc-3 that was obtained by successively culturing human liver cell cancer Hc-3 under the skin of a nude mouse for successive culture, making the tumor into a 1 mm to 2 mm square piece of tissue, and transplanting it to the liver by inserting a transplantation needle under the costal arch of the right flank region of a nude mouse for transplantation."

E. Comparison and differences

Comparing Exhibit Otsu 14 Invention and the Mouse in This Action, the "tumor of the second generation of human liver cell cancer Hc-3 that was obtained by successively culturing human liver cell cancer Hc-3 under the skin of a nude mouse for successive culture" of Exhibit Otsu 14 Invention is equivalent to the "tumor tissue of human bowel cancer line TK-4, which is obtained from human bowel cancer and has high metastatic property that has been maintained by a method of successive culture under the skin (however, this was established in 1993 from the pathological

lesion in the involved liver of a Japanese male aged 50 who was affected by sigmoid colon cancer at Second Department of Surgery, Hamamatsu University School of Medicine)." In what follows, "1 mm to 2 mm square piece of tissue" is equivalent to "120 mg piece (mass) of tumor," "nude mouse for transplantation" is equivalent to "male nude mouse aged six weeks (BALB/c nu/nu: Clea Japan, Inc.)," "transplanting it to the liver by inserting a transplantation needle under the costal arch of the right flank region [of a nude mouse for transplantation]" is equivalent to "orthotopic transplantation by sewing, with a 6-0 Polysorb suture (made by Tyco Healthcare), to the cecal wall [of a male nude mouse aged six weeks (BALB/c nu/nu: Clea Japan, Inc.)]," and "animal model" is equivalent to "nude mouse," respectively. Then, lung metastasis was recognized in the nude mouse of Exhibit Otsu 14 Invention.

However, there is no explicit statement that the lung metastasis in the nude mouse of Exhibit Otsu 14 Invention is the metastasis of liver cancer in a non-human animal model. Therefore, Exhibit Otsu 14 Invention has a difference from the Mouse in This Action in that it is unclear whether it is a non-human animal model for the metastasis of human neoplastic disease.

F. Whether or not a person ordinarily skilled in the art can easily conceive of the structure of the Mouse in This Action

As mentioned in C. above, it is stated in Exhibit Otsu 27 that a ball-like metastasis of approximately 2 mm in diameter was recognized in the lower lobe of the right lung due to the transplantation of the second generation of liver cancer tumor obtained by successively culturing a piece of human liver cancer tissue in a nude mouse to the liver of a nude mouse (line 18 in the right column of page 31 to line 7 in the right column of page 32). After that, it is stated therein that this clearly proved that liver cell cancer transplanted to the liver caused lung metastasis (lines 11 to 19 in the left column of page 33). Therefore, Exhibit Otsu 27 is recognized as disclosing the knowledge that a nude mouse (animal model) in which lung metastasis occurs can be obtained through orthotopic transplantation of a piece of human liver cancer tissue to the liver of a nude mouse, which is the original organ.

In light of the following, it is recognized that a person ordinarily skilled in the art who sees Exhibits Otsu 14 and 27 can easily conceive of the structure of the Mouse in This Action by applying the knowledge stated in Exhibit Otsu 27 to Exhibit Otsu 14 Invention: [i] Exhibit Otsu 14 Invention and Exhibit Otsu 27 Invention fall within the same technical field wherein an animal model is made through orthotopic transplantation, to a nude mouse, of a mass of tumor tissue obtained by successively transplanting a piece of liver tumor tissue taken from the liver of a liver cancer patient under the skin of a nude mouse, and in that technical field, it was considered as a common technical problem to generate a human animal model that can reproduce the metastatic process as of the priority date of the Application; [ii] Regarding the part concerning the fact that lung metastasis was recognized in a nude mouse that is directly related to said technical problem,

Exhibit Otsu 14 quotes Exhibit Otsu 27 as a reference document.

G. Summary

On these bases, the Mouse in This Action is one which a person ordinarily skilled in the art could have easily presumptively conceived of based on publicly known art as of the priority date of the Application, and it does not fulfill the fourth requirement of the doctrine of equivalents.

(2) Regarding the allegations of the appellant

A. Regarding Exhibit Otsu 14

(A) Regarding the mice

The appellant alleges that, in Exhibit Otsu 14 Invention, nude mice are not distinguished by sex and their weekly ages are also not unified.

However, it is inappropriate, solely based on the fact that there is by chance a statement, "male and female," in Exhibit Otsu 14, to consider that a person ordinarily skilled in the art would understand that experiment was carried out in Exhibit Otsu 14 Invention while mixing female and male mice so that the mice are free to reproduce themselves. Moreover, it is also not recognized that the weekly ages of the nude mice especially lack unity.

The aforementioned allegation of the appellant is unacceptable.

(B) Regarding pieces of tissue

The appellant alleges that the size and quantity of the transplanted pieces of tumor tissue are not specified in Exhibit Otsu 14 Invention. However, in light of the statements in Exhibit Otsu 14 and the purpose of successive culture in relation to transplantation to the liver of a nude mouse, it is not recognized that the size and quantity of the transplanted pieces of tissue is not specified.

Therefore, the aforementioned allegation of the appellant is unacceptable.

(C) Regarding orthotopic transplantation and liver tumor

The appellant alleges that it cannot be said based on Exhibit Otsu 14 that a piece of tumor was transplanted to the liver of a nude mouse and that it is also unclear whether a liver tumor occurred due to transplantation.

However, Exhibit Otsu 14 clearly specifies the actual existence of a liver tumor by stating as follows: "(lines 6 in the right column of page 41 to line 23 of page 42) … Transplantation to the liver by inserting a transplantation needle under the costal arch of the right flank region was carried out for 10 mice, but it succeeded only in two mice, specifically, the second generation of Hc-3 and the third generation of Hc-5. Transplantation to the liver by laparotomy was carried out for two mice with the sixth generation of Hc-4. The transplanted tumor took in both of those mice, however, … slaughtered. For all of those four mice, existence of a liver tumor was confirmed after slaughter. In addition, lung metastasis of the second generation of Hc-3, which was transplanted under the right costal arch, was recognized." Therefore, it is obvious that a piece of tumor was also transplanted to the liver by a transplantation method wherein a piece of tumor

tissue was transplanted with a transplantation needle so that it contacts the lateral segment of the right lobe of the liver.

Therefore, all of the aforementioned allegations of the appellant are unacceptable.

(D) Regarding metastasis

The appellant alleges that whether or not the growth of tumor outside the liver is due to metastasis cannot be determined based on Exhibit Otsu 14.

However, it is stated in Exhibit Otsu 14 that "a 1 mm to 2 mm square piece of tissue …" was transplanted "with a transplantation needle whose external diameter is 2.5 mm to 1.5 mm." In light of the statements in page 66 of Natsume Seisakusho Co., Ltd.'s catalog of animal experiment equipment (Exhibit Otsu 24), the internal diameter of a transplantation needle whose external diameter is 2.5 mm and 1.5 mm is recognized as 2.0 mm and 1.1 mm, respectively. Then, in Exhibit Otsu 14, there is no statement suggesting that a piece of tumor tissue that is bigger than the external diameter of the transplantation needle is implanted. In that case, it is natural for a person ordinarily skilled in the art who sees Exhibit Otsu 14 to understand that the purpose of the aforementioned statement in Exhibit Otsu 14 is to state that a transplantation needle that fits into the size of the piece of tumor to be transplanted is used when transplanting a 1 mm to 2 mm square piece of tissue with such transplantation needle.

Moreover, a piece of tumor tissue is elastic, and its external form is neither destroyed nor remains markedly-deformed even if it is physically compressed with tweezers. Furthermore, a 1.5 mm piece of tumor tissue is recognized as maintaining its shape as a mass even after the operation wherein it is retained in the inside of a mantle needle whose external diameter is approximately 1.5 mm and internal diameter is 1.1 mm and is pushed out with an inner push stick (Exhibit Otsu 26). Therefore, where a piece of tumor tissue is transplanted with a transplantation needle according to the ordinary operation method, it is quite unlikely for a small piece of tumor cell or tumor tissue separated from the piece of tumor tissue to be emitted.

Then, the following are clearly stated in Exhibit Otsu 14: "lung metastasis was recognized" (lines 22 to 23 in the left column of page 42); "Metastasis was seen in only one mouse wherein an invasive tumor was formed in the liver, and it was to the lung" (lines 14 to 15 in the right column of page 48). Therefore, it is natural to consider that existence of a tumor in the lung of the nude mouse to which a piece of tumor tissue was transplanted in the liver, as mentioned above, suggests that the tumor of the nude mouse transplanted to the liver thereof had metastasized to the lung. Incidentally, if a piece to be transplanted was transplanted from the liver side to the lung due to an erroneous operation of the transplantation needle, the nude mouse would have died immediately (see Exhibits Ko 77, 78-1, and 78-2).

On these bases, the aforementioned allegation of the appellant is unacceptable.

(E) Regarding the number of cases of metastasis

The appellant alleges that nude mice wherein a tumor metastasized to the lung are too few. However, pieces of liver tumor tissue transplanted to the ten nude mice were not taken from the same patient and were successively cultured under the skin of nude mice. Therefore, the allegation of the appellant is erroneous in its premise and is thus unreasonable.

B. Regarding Exhibit Otsu 27

(A) Regarding the term "rats"

The appellant alleges that ordinary rats to which transplantation is impossible were used for the transplantation method of Exhibit Otsu 27.

However, in Figures 1 and 2 that are quoted in the part where the term "rats" is used (line 18 in the right column of page 31 to line 7 in the right column of page 32), the term "nude mice" is used. In addition, there is the following statement in the Summary section of Exhibit Otsu 27: "We reported our success in the transplantation of human liver cancer to the liver of a nude mouse. The tumor transplanted to the liver was slightly different from one transplanted under the skin in terms of the mode of development, and it had no tumor fibrous capsule and had caused lung metastasis" (lines 1 to 4 in the right column of page 33). Moreover, looking at the entirety of Exhibit Otsu 27, it is obvious that the subject of transplantation are nude mice, and the term "rats" in Exhibit Otsu 27 is considered as an obvious and simple erroneous description of the term "nude mice," including the statements in parts other than the aforementioned parts (lines 11 to 14 in the right column of page 31).

Therefore, the aforementioned allegation of the appellant is unacceptable.

(B) Regarding the transplantation method

The appellant alleges that the transplantation method of Exhibit Otsu 27 is unclear.

However, the transplantation method is obvious because there is the following statement in Exhibit Otsu 27: "(lines 25 to 28 in the left column of page 31) Regarding the transplantation method, liver cancer tissue taken by resection or with a needle was made into a 2 mm square piece of tissue in physiological saline water, and was transplanted under the skin of the abdominal or dorsal regions on both sides (near the lateral segment of the liver on the right side) with a transplantation needle."

Therefore, the aforementioned allegation of the appellant is unacceptable.

(C) Regarding metastasis

The appellant alleges that metastasis cannot be confirmed in Exhibit Otsu 27.

However, Exhibit Otsu 27 clearly describes occurrence of lung metastasis by stating as follows: "(lines 16 to 19 in the left column of page 33) there is the possibility that a tumor will present similar metastasis if it is transplanted to the original organ. We would like to think that the fact that our liver cell cancer transplanted to the liver caused lung metastasis had clearly proven such possibility"; "(line 4 in the left column of page 32 to line 1 in the right column

thereof) a ball-like metastasis of approximately 2 mm in diameter was recognized in the lower lobe of the right lung."; "(lines 2 to 5 in the left column of page 33) in our liver transplantation examples, … it was accompanied by lung metastasis." In addition, it is natural to consider that existence of a tumor in the lung of a nude mouse to which a tumor was transplanted in the liver suggests that the tumor transplanted to the liver of the nude mouse had metastasized to the lung. Incidentally, if a piece to be transplanted was transplanted from the liver side to the lung due to an erroneous operation of a transplantation needle, the nude mouse would have died immediately (see Exhibits Ko 77, 78-1, and 78-2).

Therefore, the aforementioned allegation of the appellant is unacceptable.

(3) Summary

Consequently, infringement under the doctrine of equivalents is not established in relation to the Mouse in This Action.

5. Summary

According to 2. or 3. above, literal infringement is not established in relation to the Mouse in This Action at any rate. According to 4. above, infringement under the doctrine of equivalents is also not established in relation to the Mouse in This Action.

Therefore, it is obvious without the need to make determinations on other points that there is no reason for the claim in question and that the claim in question should be dismissed.

No. 5 Conclusion

Therefore, the judgment in prior instance that dismissed the claim in question is reasonable, and this appeal shall be dismissed as there is no reason therefor. The judgment shall be rendered in the form of the main text.

Intellectual Property High Court, Second Division

Presiding judge: SHIMIZU Misao

Judge: NAKAMURA Kyo

Judge: NAKABU Yuki