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**Datasheet for the decision  
of 13 July 2012**

**Case Number:** T 1262/04 - 3.3.04

**Application Number:** 99124640.6

**Publication Number:** 1016419

**IPC:** A61K 49/00

**Language of the proceedings:** EN

**Title of invention:**

Non-invasive localization of a light-emitting conjugate in a mammal

**Applicant:**

The Board of Trustees of  
The Leland Stanford Junior University

**Headword:**

Non-invasive localization/LELAND STANFORD

**Relevant legal provisions:**

EPC Art. 53(a), 53(c), 54, 56, 76(1), 83, 84, 123(2)  
EPC R. 28(d)

**Relevant legal provisions (EPC 1973):**

EPC R. 23d(d)

**Keyword:**

"Main request - added matter (no), sufficiency, clarity, novelty, inventive step (yes), exclusions from patentability (no)"

**Decisions cited:**

G 0001/98, G 0001/04, G 0001/07, T 0774/89, T 0019/90,  
T 0182/90, T 0035/99, T 0315/03

**Catchword:**

-



Case Number: T 1262/04 - 3.3.04

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.04  
of 13 July 2012

**Appellant:**  
(Applicant)

The Board of Trustees of  
The Leland Stanford Junior University  
900 Welch Road, Suite 350  
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**Representative:**

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**Decision under appeal:**

**Decision of the Examining Division of the  
European Patent Office posted 13 April 2004  
refusing European patent application  
No. 99124640.6 pursuant to Article 97(2) EPC.**

**Composition of the Board:**

**Chairman:** R. Gramaglia  
**Members:** B. Claes  
R. Moufang

## Summary of Facts and Submissions

- I. The appeal was lodged by the applicant (hereinafter "appellant") against the decision of the examining division to refuse European patent application 99124640.6 with the title "Non-invasive localization of a light-emitting conjugate in a mammal" on the basis of Article 97(1) EPC 1973. The application is a divisional of the earlier European patent application 95941424.4 which was filed as international application PCT/US95/15040 on 17 November 1995 and published as WO 97/18841.
- II. The application was filed with the following independent claims:
- "1. A method for detecting eukaryotic cells in a living non-human animal, said method comprising:
- (a) providing a non-human animal comprising eukaryotic cells containing a heterologous gene construct encoding at least one light generating protein;
  - (b) placing the animal in the detection field of a photodetector device;
  - (c) maintaining the animal within the detection field of the photodetector device; and
  - (d) measuring through opaque tissue, photon emission from said cells with said photodetector device, to detect said eukaryotic cells.
9. A method for identifying a therapeutic compound effective to inhibit the growth and/or metastatic spread of a tumor, said method comprising:

(a) administering tumor cells labeled with or containing a light-generating moiety to groups of experimental and control animals;

(b) treating the experimental group with a selected compound;

(c) localizing the tumor cells in animals from both groups by imaging photon emission from the light-generating molecules associated with the tumor cells with a photodetector device; and

(d) identifying the compound as therapeutic if the compound is able to significantly inhibit the growth and/or metastatic spread of the tumor in the experimental group relative to the control group.

10. A method for identifying a therapeutic compound effective to inhibit the growth and/or metastatic spread of a tumor, said method comprising:

(a) administering tumor cells containing a heterologous gene construct encoding a light generating protein to experimental and control groups of non-human animals;

(b) treating the experimental group with a selected compound;

(c) localizing the tumor cells in animals from both groups by imaging photon emission from the light-generating molecules associated with the tumor cells with a photodetector device; and

(d) identifying the compound as therapeutic if the compound is able to significantly inhibit the growth and/or metastatic spread of the tumor in the experimental group relative to the control group.

11. A method for identifying a therapeutic compound effective to inhibit the growth and/or metastatic spread of a tumor, said method comprising:

(a) administering tumor cells containing a heterologous gene construct encoding a light generating protein to experimental and control groups of non-human animals;

(b) treating the experimental group with a selected compound;

(c) measuring photon emission from animals of both groups with a photodetector device; and

(d) identifying the compound as therapeutic if the compound is able to significantly inhibit the growth and/or metastatic spread of the tumor in the experimental group relative to the control group."

III. The following documents are specifically referred to in the present decision:

D19: Declaration by Prof. L. Cork dated 6 December 2004.

D21: Declaration by Prof. R. Cardiff dated 29 December 2003.

D22: Declaration by Prof. G. Otto dated 1 June 2004.

D28: Contag *et al.* (1995), *Molecular Microbiology* 18(4), pages 593-603.

IV. In an interlocutory decision, announced at the oral proceedings held on 7 March 2007 and dispatched in written form on 8 May 2007, the board decided that the subject-matter of claim 1 of the then main request complied with the requirements of Articles 54 and 83

- EPC 1973 and with the requirements of Article 56 EPC 1973 insofar as the documents (D1) to (D5) as cited in the reasons of the decision under appeal and documents (D6) to (D27) as cited in the statement of grounds of appeal were concerned. Document (D28) was introduced into the proceedings by the board.
- V. The board invited the appellant to submit comments relating to the exact publication date of document (D28) and its content with a communication dated 26 July 2007.
- VI. With a letter dated 13 September 2007, the appellant *inter alia* filed evidence concerning the exact date of availability to the public of document (D28) and filed a new main and an auxiliary request 1 accompanied by possible "amendments A-C" for claim 1.
- VII. On 12 October 2007 the board communicated its preliminary opinion that the claims of the new main request complied with the requirements of Articles 76(1) and 123(2) EPC 1973, that document (D28) did not belong to the state of the art pursuant to Article 54(2) EPC 1973 and that the positive findings concerning the novelty, inventive step and sufficiency of disclosure of the subject-matter of the claims relevant for the interlocutory decision of 7 March 2007 applied *mutatis mutandis* to the subject-matter of the claims of the new main request.
- VIII. With a communication dated 7 December 2007, the board informed the appellant that it considered it appropriate to delay further dealing with the case pending the outcome of at least the then pending

referral G 1/07 and possibly of the then equally pending referral G 2/06 to the Enlarged Board of Appeal.

- IX. In response to a summons to oral proceedings to take place on 6 October 2011 by the board, the appellant submitted arguments *inter alia* in relation to opinion G 1/04 and decision G 1/07 of the Enlarged Board of Appeal, and subsequently, with a letter dated 15 September 2011, new auxiliary requests 2 and 3.
- X. In a telephone conversation on 26 September 2011, the appellant was informed that preliminarily the board would be inclined to consider to order the grant of a patent on the basis of a request which combined amendments "B" and "C" as suggested in the appellant's letter dated 13 September 2007.
- XI. With a letter dated 27 September 2011, the appellant submitted a new amended **main claim request**, which was based on auxiliary request 2 filed on 15 September 2011, incorporating "Amendment B" as proposed in the letter of 13 September 2007.

The independent claims of this request read:

"1. A method for detecting **tumour** cells in a living **mouse model of human disease**, said method comprising:

(a) providing **a living, mouse** comprising **tumour** cells, **said tumour cells comprising a** heterologous **genetic** construct encoding at least one light generating protein;

(b) placing the **mouse** in the detection field of a photodetector device;

(c) maintaining the **mouse** within the detection field of the photodetector device; and

(d) measuring through opaque tissue, photon emission from said cells with said photodetector device, to detect said **tumour** cells.

8. A method for identifying a therapeutic compound effective to inhibit the growth and/or metastatic spread of a tumour **in a mouse model of human disease**, said method comprising:

(a) administering tumour cells labeled with or **comprising** a light-generating moiety to groups of experimental and control **living mice**;

(b) treating the experimental group with a selected compound;

(c) localizing the tumour cells in **mice** from both groups by **measuring, through opaque tissue**, photon emission from the light-generating **moieties** associated with the tumour cells with a photodetector device; and

(d) identifying the compound as therapeutic if the compound is able to significantly inhibit the growth and/or metastatic spread of the tumour cells in the experimental group relative to the control group.

9. A method for identifying a therapeutic compound effective to inhibit the growth and/or metastatic spread of a tumour **in a mouse model of human disease**, said method comprising:

(a) administering **eukaryotic** tumour cells **comprising** a heterologous **genetic** construct encoding a light generating protein to experimental and control groups of **living, mice**;

(b) treating the experimental group with a selected compound;



(c) localizing the tumour cells in **mice** from both groups by **measuring, through opaque tissue**, photon emission from light-generating **proteins** associated with the tumour cells with a photodetector device; and

(d) identifying the compound as therapeutic if the compound is able to significantly inhibit the growth and/or metastatic spread of the tumour cells in the experimental group relative to the control group.

10. A method for identifying a therapeutic compound effective to inhibit the growth and/or metastatic spread of a tumour **in a mouse model of human disease**, said method comprising:

(a) administering **eukaryotic** tumour cells **comprising** a heterologous **genetic** construct encoding a light generating protein to experimental and control groups of **living mice**;

(b) treating the experimental group with a selected compound;

(c) measuring photon emission **through opaque tissue** from **mice** of both groups with a photodetector device; and

(d) identifying the compound as therapeutic if the compound is able to significantly inhibit the growth and/or metastatic spread of the tumour cells in the experimental group relative to the control group."

Emphasis added by the board highlights the differences with claims 1 and 9 to 11 as originally filed.

Claims 2 to 7 and 11 to 27 were dependent on one or more of the independent claims. In particular claim 6 read:

"6. The method of any of Claims 1 to 5, wherein the mouse is a transgenic mouse comprising tumour cells, said cells comprising a heterologous genetic construct encoding at least one light generating protein."

XII. On 29 September 2011 the board cancelled the oral proceedings.

XIII. The appellant's arguments be summarised as follows:

*Added matter (Articles 76(1) and 123(2) EPC)*

- The compliance with Article 76(1) EPC of the claims as originally filed had been addressed in the letter dated 10 December 1999, which had been submitted upon filing of the present divisional application. Further specific support could be found in the application as filed.
  
- The term "mouse model of human disease" found a general basis in the application as filed on page 47, lines 17 to 18. The fact that the claims were now limited to methods used in mice found support in general in the application and in particular in the examples. Mice were a well known laboratory animal and one in which benefit to mankind in conducting cancer research was well established. By their very nature animal models of human disease were limited to established laboratory animals whose use was regulated in a manner to ensure appropriate welfare of the animal and justification for performing animal research.

- The amendment to qualify the tumour cells in claims 8 to 10 as "eukaryotic" tumour cells found a basis in the application as filed on page 21, lines 35 to 37.

*Sufficiency of disclosure, novelty and inventive step*

- The journal containing document (D28) had been catalogued and made available at the British Library on 18 December 1995. As evidence a copy of the British Library copy of the cover of the journal was submitted showing the library date label. The same journal was date-stamped by the Stanford University Medical Center library in the United States, on 28 December 1995, which could be taken from the further evidence submitted. The relationship between the two dates implies that both copies were posted around the same time, shortly before 18 December 1995. The filing date of the application, 17 November 1995, was more than one month before public availability of document (D28) at the British Library and five weeks prior to availability at the Stanford library. Document (D28) was thus not contained in the prior art.

*Article 53(a) EPC*

- Rule 28(d) EPC (corresponding to Rule 23d(d) EPC 1973) was specifically directed to "processes for modifying the genetic identity of animals" and was thus not of relevance to method claims 1-5 or 7-27 which were not necessarily applied to transgenic animals. It was irrelevant here whether or not these

claims "encompassed" transgenic animals. Only claim 6 applied to transgenics.

- Though in decisions T 315/03 and T 606/03 the boards had interpreted Rule 23d(d) EPC 1973 as requiring a "balancing act" test, it was beyond the capacity of the EPO to make a meaningful determination of this issue.
  
- Where an applicant made a *prima facie* case that a claim which involves modifying the genetic identity of a non-human animal has any potential medical benefit to man, this should be sufficient to meet the requirements of Rule 28(d) EPC. Only where the process was clearly so abhorrent that any practice of it would clearly be unacceptable under any circumstances should Rule 28(d) EPC apply.
  
- In the field of tumour drug development, it was clearly plausible that testing cancer therapeutics would identify or help the development of a drug that benefits patients in a clinical setting. Furthermore, animal experiments had to be carried out for the development of new drugs and treatments. Any animal model which related to a new and useful means for developing, improving or validating tumour therapies clearly had the potential to be of substantial benefit to man and met the requirements of Rule 28(d) EPC unless the suffering to the animal was clearly and evidently so abhorrent that the production or use of the model would be inconceivable.

- Evidence was on file from a number of experts in the field that the methods of the present invention were currently used and useful in medical research.
  
- The use of the invention was not contrary to morality or *ordre public*. Medical benefit was readily apparent and set out in the patent application as published in paragraph [0176], i.e. it is a non-invasive method which is broadly applicable and may also enable temporal and spatial evaluation of, for example, tumour progression in living mammals, and have application in pharmaceutical development and screening. Widespread use of in vivo imaging might reduce the numbers of animals and the time needed for experiments. Reducing the numbers of animals, and also providing non-invasive means for their study, was designed to reduce animal suffering as well as providing benefit to man.

With respect to the claims of previous requests (see for example section II, above), the following further arguments were provided:

- When holding that the claims should be limited to mice, and not animals or even rodents in general in view of Rule 23d(d) EPC 1973, the board deciding case T 315/03 had wrongly reversed the normal burden of the EPO to show basis for an objection and placed the onus on the patentee to show that each and every animal embraced by the term "rodent" would suffer by being made transgenic in accordance with that invention. On the one hand, there had been no evidence before the board that, for example, an

"onco-squirrel", if made transgenic, would suffer any more or less than a mouse, nor that the benefit to man would be any less. Secondly, a large number of animals were used in medical research, including but not limited to mice, rats, guinea pigs, cats, dogs, and various primates. Any animal experiments, being tightly regulated, were unlikely to be authorised in the first place without evidence of any benefit. On the other hand, the board took the view, that all conceivable uses of the "oncomouse" would provide a contribution to cancer studies, and that all other "oncorodents" would have no conceivable benefit under any circumstances. The board however offered no evidence to support the latter finding. Given that rats, guinea pigs and hamsters are all rodents widely used in research, and that non-research rodents were likely to have very similar physiology to their laboratory cousins, the finding concerning the notion of rodents seemed surprising and contrary to the presumption the EPO should grant patents unless the office provided well-founded reasons not to do so.

- It was furthermore contrary to every other tenet of patent law to divide a claim relating to an animal into a notional Noah's Ark of each and every animal. Decision G 1/98 of the Enlarged Board of Appeal had expressly rejected when considering whether or not a claim related to a "plant variety". The consequence was that the relevant question to be asked was rather whether the claim as such (if indeed Rule 23d(d) applied), related to something likely to provide any medical benefit within its scope. If the

answer was "yes", then the requirements of Article 53(a) EPC were met.

*Article 53(c) EPC*

- The method of claim 1 only referred to the collection of data. It provided intermediate results, e.g. information about the localisation of a cell in the body. It did not include the comparison of this information with a standard nor the finding of any significant deviation (a symptom) or the attribution of the deviation to a particular clinical picture. Claim 1 was therefore not a diagnostic method in line with the finding in opinion G 1/04 of the Enlarged Board of Appeal and decisions T 9/04 and T 143/04.
  
- A person skilled in the art performing the invention of claim 1 knew that such tumour cells were in the mouse because such cells would have to have been introduced or generated as part of an experimental test system. The method claimed was thus not performed to diagnose, *stricto sensu*, whether or not the non-human mammal had a tumour, but merely to locate where such a tumour was located, or its size or rate of growth, etc. Such an activity was not "*the diagnosis for curative purposes stricto sensu*" within the meaning of opinion G 1/04, but merely the gathering of data for research. The method of claim 1 provides hence only intermediate results, e.g. information about the localisation of a cell in the body. It did not include the comparison of this information with a standard nor the finding of any

significant deviation (a symptom) or the attribution of the deviation to a particular clinical picture.

- Claims 8-10 were directed to assay methods conducted on test animals (mice) to determine the efficacy or otherwise of a test compound and included the step of administering tumour cells to an animal such as to allow the tumour cells to grow and/or spread in a test animal. The presence of this step was the complete opposite of therapeutic – it was to induce a potentially fatal growth in the test animal.
  
- The various kinds of medical treatments covered in Article 53(c) EPC (corresponding to Article 52(4) EPC 1973) had the primary purpose to achieve an improved state of the health of the human or animal body and not the destruction of the organism. The present claims were directed to research methods for the development of pharmaceuticals and in principle were no different from other research methods for this purpose which are legitimately the subject of patent protection.
  
- As noted in decision T 774/89, the purpose of therapy was invariably to restore an organism from a pathological to its original condition, or to prevent a pathology in the first place. The introduction of tumour cells in a test animal in contrast was to induce a pathology. In decision T 182/90 it was furthermore held that methods consciously ending in the laboratory animal's death were not in their nature methods of surgical treatment. The board equally applied this reasoning to diagnostic methods, as the animal body on which



it is practised did not survive. In any test procedure involving the introduction of tumour cells in a test animal, it would be in accordance with normal standards to sacrifice the animal following data collection.

- These findings were also endorsed in decision G 1/07 of the Enlarged Board which stated that procedures whose conscious (deliberate or incidental) end result is the death of the living being under treatment do not qualify as methods in which maintaining the life and health of the subject is of paramount importance (see point 3.3.5. of the reasons).
  
- Present claims 8 to 10 were essentially assay methods conducted on test animals to determine the efficacy or otherwise of a test compound. Such methods did not fall within the medical sphere, but were equivalent to other laboratory research methods. The paramount consideration when carrying out such methods was to achieve a consistent and reliable assessment of the compounds being tested and not to maintain the life and health of the test animals.

XIV. The applicant (appellant) requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 27 of the main request filed with letter dated 27 September 2011. The appellant requested furthermore that the case be remitted to the department of first instance for the adaptation of the description.

## Reasons for the Decision

*Added matter (Articles 76(1) and 123(2) EPC)*

1. Neither during the examination proceedings nor in the decision under appeal the examining division has expressed a negative or an explicit positive opinion on the compliance of the claims with respect to the requirements of Articles 76(1) and 123(2) EPC.
  
2. The description of the parent application as filed is identical to the description of the present divisional application. Therefore identification of support for the claimed subject-matter in the description of the parent application implies a positive finding of compliance of the claims with both Article 76(1) and 123(2) EPC. In the following the board will thus merely refer to the relevant passages in the description of the parent application as originally filed.
  - 2.1 A general basis for independent claim 1 is found on page 5, lines 19 to 24. Further details are for example disclosed on page 1, lines 6 to 9, page 2, line 5 to page 3, line 24, page 9, lines 35 to 37. The description furthermore discloses eukaryotic cells as biocompatible entities to be used (page 2, line 8; page 10, line 5 and page 21, lines 35 to 37) and that these cells may comprise a "heterologous genetic construct" that provides for a light-generating moiety (page 22, lines 2 to 4). That these cells may be tumour cells finds a basis on page 23, line 33 to page 24, line 6. In addition, the section "Immobilizing the subject" (see page 30) discloses that the animal can be placed and maintained in the detection field of a

photodetector device. It is also described that the measurement of photon emission may be effected through opaque tissue (page 5, lines 19 to 24 and page 8, lines 31 to 36).

2.2 The method of claim 1 is to be implemented in a "mouse model of human disease". A literal basis for the term "animal model of human disease" in the context of the invention can be found on page 47, lines 17 to 18, of the description. The board is furthermore convinced that the skilled person reading the originally filed description as a whole would clearly and unambiguously understand that the disclosed methods of the invention based on bioluminescence technology primarily serve the purpose of elucidating the development of diseases and the effects of pharmaceutical treatment in experimental animals and that particular emphasis is placed on animal models for tumour research. In this respect, the following passages can be mentioned: page 1, lines 31-32; page 3, lines 25-28; page 6, lines 7-20; page 44, lines 17-22; page 45, line 32, to page 46, lines 21. It is also noted that mice are the experimental animals to be used according to the examples (see Examples 5-11).

2.3 Claims 2 to 7 depend directly or indirectly on claim 1. For claim 2 a basis can be found on page 32, line 30 to page 33, line 31, of the description; for claim 3 on page 33, line 32 to page 34, line 2; for claim 4 on page 11, lines 3 to 9 and page 33, lines 20 to 31; for claim 5 on pages 30 and 31 under the heading "Immobilizing the subject"; for claim 6 on page 24, section IV entitled "Transgenic Animals Containing Genes Encoding Light-Generating Proteins"; and for claim 7 on page 23, lines 16 to 17 and lines 35 to 36.

2.4 Independent claim 8 finds a basis on page 6, lines 7 to 20.

2.5 Independent claim 9 is likewise based on page 6, lines 7 to 20 whereby the light-generating moiety has been specified to be a protein encoded by a heterologous gene which is supported by page 21, line 37 to page 22, line 4 in combination with page 23, lines 33 to 35 and page 46, lines 16 to 21.

2.6 Likewise, independent claim 10 is based on the same passages as independent claim 9 whereby feature (c) has been reworded in line with, *inter alia*, the corresponding passage on page 31, lines 25 to 30.

2.7 Claims 11 to 27 depend directly or indirectly on one or more of the independent claims. A basis for claim 11 is found on page 10, lines 7 to 9; for claim 12 on page 23, lines 7 to 9, for claim 13 on page 23, lines 9 to 12; for claim 14 on page 23, lines 16 to 25 and page 24, lines 3 to 6; for claim 15 on page 10, lines 11 to 12 and page 14, lines 6 to 23; for claim 16 in the section "Bioluminescence-based moieties" starting on page 15; for claim 17 on page 2, lines 16 to 19 and page 14, lines 6 to 23, for claim 18 on page 15, line 22 to page 17, line 19; for claim 19 on page 12, lines 28 to 30; for claim 20 on page 16, lines 4 to 10, for claim 21 on page 11, lines 18 to 23, for claim 22 on page 10, line 34 through page 11, line 2 and on page 27, line 32 to page 38, line 9, for claim 23 on page 10, lines 34 to 37 and page 28, lines 34 to 37, for claim 24 on page 29, lines 28 to 30; for claim 25 on page 29, lines 28 to 30; for claim 26 on page 30,

lines 22 to 28 read in conjunction with the support for claims 25 and 26; and for claim 27 for example on page 1, lines 6 to 9 of the application as filed in the section "Field of the invention".

3. In view of the above considerations the board is satisfied that the claims comply with the requirements of Articles 76(1) and 123(2) EPC.

*Article 84 EPC*

4. In the decision under appeal the examining division did not raise any objections under Article 84 EPC, nor does the board see any reason for doing so in respect of the present claims.
5. In particular, a skilled reader would readily understand the term "**mouse model of human disease**" as implying that the methods of the invention are to be performed on mice only with the aim of investigating the development and pharmacological treatment of human diseases. These diseases are further specified in the claims as being tumours. Furthermore the skilled reader would understand that the animals involved have to be experimental animals which are conventionally used in cancer research. The board is therefore satisfied that this term is clear to a skilled person.
6. In view of the above considerations, the board considers that the claims meet the requirements of Article 84 EPC.

*Sufficiency of disclosure, novelty and inventive step*

7. In its interlocutory decision dated 7 March 2007 and dispatched in written form on 8 May 2007, the board has already decided that the subject-matter of claim 1 of the then main request complied with the requirements of Articles 54 and 83 EPC 1973 and with the requirements of Article 56 EPC 1973 insofar as the documents (D1) to (D5), as cited in the reasons of the decision under appeal, and documents (D6) to (D27), as cited in the statement of grounds of appeal, were concerned. The board however reserved its decision with respect to the issue whether the document (D28) could be detrimental to the inventive step of the claimed subject-matter.
8. The positive findings of the interlocutory decision also apply to the more restricted subject-matter of claim 1 of the appellant's main request. They also apply *mutatis mutandis* to the subject-matter of the further independent claims 8 to 10 and of all the dependent claims.
9. When the board introduced document (D28), it appeared that its publication had occurred around the relevant date claimed for the present application. Since, however, the exact publication date could not be unambiguously established at the date of oral proceedings before the board, the appellant was given an opportunity to submit further evidence in this respect.
10. The appellant filed two documents showing the dates when the document (D28) was received at major libraries.

The British Library's copy of the cover of the relevant journal issue bears the receipt date of 18 December 1995, the Stanford University Medical Center library's copy of the first page of document (D28) bears the even later date of 28 December 1995.

11. There is therefore no evidence before the board that the publication of the relevant issue of the journal occurred before the filing date claimed for the present application, i.e. 17 November 1995. On the contrary, evidence is on file that the document (D28) was available at two major libraries only more than one month after that date. The board therefore considers that it is not established that document (D28) belongs to the prior art within the meaning of Article 54(2) EPC.
12. The board concludes that the claimed subject-matter satisfies the requirements of Articles 54, 56 and 83 EPC.

*Article 53(a) EPC*

13. Independent claim 1 relates to a method for detecting tumour cells in a living mouse model of human disease which includes, *inter alia*, the step of providing a living mouse comprising tumour cells which comprise a heterologous genetic construct encoding at least one light-generating protein. Dependent claim 6 specifies that the mouse may be a transgenic mouse comprising tumour cells (see above, section XI). While such a method does not directly embrace the step of introducing the tumour cells into the mice, it presupposes, however, this step. Independent claims 8

- to 10 relate to methods for identifying therapeutic compounds which include administering tumour cells to experimental and control groups of living mice. These tumour cells are labelled with or comprise a light-generating moiety or a heterologous genetic construct encoding a light generating protein. Independent claims 8 to 10 also include a monitoring step concerning the growth and/or metastatic spread of the tumour cells in the experimental group relative to the control group.
14. The board considers that in view of the above-described character of the claimed subject-matter an examination of whether or not the patent exclusion contained in Article 53(a) EPC applies is required. The provision stipulates that European patents shall not be granted in respect of inventions the commercial exploitation of which would be contrary to "ordre public" or morality. Rule 28(d) EPC furthermore specifies that processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal shall not be patented in accordance with Article 53(a) EPC.
15. Earlier decision T 315/03 (OJ EPO 2006, 15) has dealt extensively with the interpretation of Article 53(a) and Rule 23d(d) EPC 1973 (corresponding to Rule 28(d) EPC) in the context of an invention which concerned the production of transgenic animals having an increased probability of developing neoplasms by the introduction of an activated oncogene sequence into the genome of a rodent. It came *inter alia* to the following conclusions:



- Rule 23d(d) EPC 1973 applied to a case which was pending on the date when the rule took effect.
  - In cases falling within Rule 23d(d) EPC 1973, a further or additional objection under Article 53(a) EPC 1973 based on the balancing test developed in decision T 19/90 (OJ EPO 1990, 476) could be raised.
  - A case not falling within one of the categories listed in Rule 23d EPC 1973 had to be considered further under Article 53(a) EPC 1973.
16. The method according to independent claims 8 to 10 include the administration of specifically prepared tumour cells (which may be genetically modified) to living mice and the monitoring of the growth and/or metastatic spread of these tumour cells. The facts of the present case are thus similar to those underlying decision T 315/03 (*supra*), in that the claimed method involves the deliberate generation of tumours in animals. Nevertheless, a substantial difference is that, in contrast to the invention dealt with in decision T 315/03 (*supra*), the methods of claims 8 to 10 do not involve the modification of the genome of the animals themselves. Therefore, the patent prohibition of Rule 28(d) EPC which concerns processes for modifying the genetic identity of animals cannot be applied directly in respect of the subject-matter of claims 8 to 10. In respect of this subject-matter the question thus arises whether in the present case the test of Rule 28(d) EPC should be applied *per analogiam* and/or whether the balancing test developed in decision T 19/90 (*supra*) and endorsed by decision T 315/03 (*supra*) should be applied under Article 53(a) EPC. In

fact, as explained in more detail in decision T 315/03 (*supra*, see points 10.5 to 10.10 of the reasons), these two tests are not wholly identical. The board considers however that there is no necessity to decide in the present case whether both tests have to be applied cumulatively or which of the two tests has to be applied since both tests lead here to the same result (see point 22, below).

17. Independent claim 1 of appellant's request includes the step of providing a living mouse comprising tumour cells which comprise a specific heterologous genetic construct. While the claim does not specify how the mouse which is to be provided was generated, claim 6 which is dependent on it specifies that the mouse may well be a transgenic mouse. It thus appears that certain embodiments of the subject-matter of claim 1 presuppose preceding processes for modifying the genetic identity of animals and therefore have to be assessed under Rule 28(d) EPC. Nevertheless, the test developed in T 19/90 (*supra*) is arguably also of relevance in respect of these embodiments (see point 15, above) and in respect of those embodiments of claim 1 not relating to the provision of transgenic mice (see point 16, above).
18. Accordingly the board examines whether the subject-matter of the independent claims 1 and 8 to 10 complies with both the tests as laid down in Rule 28(d) EPC and as developed in decision T 19/90 (*supra*) under Article 53(a) EPC.
19. The board is convinced that the deliberate introduction of tumour cells into mice (which is either an explicit

step of the claimed methods or is presupposed by them), in particular with the aim of monitoring their growth or metastatic spread, is most likely to cause suffering to these animals. This is in line with the view taken in decision T 315/03 (supra) concerning the deliberate introduction of an activated oncogene into the genome of rodents.

20. The wording of the claims and the description of the patent application make it abundantly clear that the claimed methods are performed in the framework of cancer research. The main purpose is the identification and study of (putative) anti-tumour compounds, thus offering the prospect of a valuable contribution to medical research.
21. Furthermore, the appellant submitted several documents in order to support its view that the methods of the claimed invention are likely to produce a substantial medical benefit to man or animal.
  - 21.1 Document (D19) is a declaration by Prof. Linda C. Cork, stating that a significant benefit of the optical imaging technology was enabling scientists to observe mechanisms of action or cascading events within the animal. These events would not otherwise be detected using conventional imaging methods. The technology was particularly important in drug studies where biological pathways involving multiple tissues and organs interacted with the drug in a manner that cellular systems or other *in vitro* systems did not. Prof. Cork expressed the opinion that the developed non-invasive imaging methods could greatly accelerate human medical research, including drug discovery efforts.

21.2 In document (D21), a declaration by Prof. Robert D. Cardiff, it is stated that from the viewpoint of cancer research, the use of in vivo optical imaging in animal studies had been a tremendous biomedical advance. In particular, the use of luciferase as a marker of biological function was a rapid and accessible modality that had already made a significant impact on drug discovery. Since the biological process could be observed within the animals, fewer animals were required for each study with far less suffering during their lifetimes as compared to traditional approaches to animal models of human disease. Any technology that minimized the number and suffering of animals were to be encouraged.

21.3 In document (22) Prof. Glen Otto declares that the nature of the experiments described in the application was such that the potential medical benefits of the experimentation far outweigh any potential distress caused to the animals. Whereas most drug discovery efforts required death of one or more animals at each time point, the experiments described in the application were non-invasive and allowed sequential data collection from smaller numbers of animals.

22. In view of the above, the board concludes that the claimed methods of the invention are at least likely to be of substantial medical benefit to man, thus fulfilling the criterion provided for in Rule 28(d) EPC for escaping the patent exclusion. Likewise, when applying the balancing test as developed in T 19/90 (*supra*), the board considers that this likelihood of substantial medical benefit demonstrates the

invention's usefulness to mankind in human cancer research. The board notes in addition that the appellant's credible assertion that the claimed methods lead to a reduction of the number of experimental animals in cancer research is a further relevant factor in this balancing exercise.

23. The board notes lastly that the appellant has restricted the claimed methods to their implementation in mouse models of human diseases, i.e. to conventionally accepted experimental animals. Since the claims do not embrace any other animal, the board considers that they do not cover animals for which the tests provided in Rule 28(d) EPC and developed by decision T 19/90 (*supra*) might arguably not be complied with. Accordingly, in view of this restriction, the appellant's arguments previously submitted in order to defend a broader version of the claim requests do not require to be addressed by this board.

24. The board concludes that the requirements of Article 53(a) EPC are met.

*Article 53(c) EPC*

25. According to Article 53(c) EPC European patents shall not be granted in respect of methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body. In the present case, it may be argued that the claimed methods which are performed on the animal body fall within at least one of these alternatives of excluded medical methods for the following reasons.

26. With respect to the exclusion of surgical methods the board notes that independent claims 8 to 10 contain the step of administering tumour cells to living mice, which may be via injection (see paragraph [0099] of the application as published). Furthermore, dependent claim 5 refers to the immobilization of mice in the detection field of the photodetector device. According to the description, the mouse can be immobilized by, for example, an anaesthetic (see paragraph [0121] of the application as published). Anaesthesia can be performed by injecting the animals intraperitoneally with nembutal (see paragraph [0193] of the application as published).
  
27. With respect to the exclusion of therapeutic methods it is noted that, according to step (b) of independent claims 8 to 10, the experimental group of mice is treated with a selected compound and that, according to step (d) of the claims, this compound is identified as therapeutic if it is able to significantly inhibit the growth and/or metastatic spread of the tumour cells in the experimental group relative to the control group.
  
28. With respect to the exclusion of diagnostic methods, the board notes that independent claims 1 and 8 to 10 involve the measuring of photon emission from or the detection or localization of tumour cells in the living mice.
  
29. However, as correctly pointed out by the appellant, the claimed methods do not have the purpose of improving or restoring the health of the animals involved but are to be performed in the context of experimental animals. The methods either include or presuppose that tumour

cells are deliberately administered to the test animals in order to induce a pathology. It is furthermore in accordance with normal standards to sacrifice the experimental animal following data collection (see also paragraph [0194] of the patent application as published which gives details on euthanasia protocols).

30. In its opinion G 1/04 (OJ EPO 2006, 334), the Enlarged Board dealt with the interpretation of the exclusion of diagnostic methods from patentability. One of its conclusions was that in order to fall under the patentability prohibition a claim had to include the features relating to (i) the diagnosis for curative purposes *stricto sensu*, (ii) the preceding steps which are constitutive for making that diagnosis, and (iii) the specific interactions with the human or animal body which occur when carrying those out among these preceding steps which are of a technical nature. It follows from this conclusion that a method which has no curative purpose at all cannot be regarded as a diagnostic method within the meaning of Article 53(c) EPC (see also point 6.4 of the reasons which state: "*From the fact that Article 52(4) EPC [i.e. Article 52(4) EPC 1973 corresponding to Article 53(c) EPC] further refers to methods of surgery and therapy it can be inferred that these diagnostic methods serve curative purposes ...*").
31. In its decision G 1/07 (OJ EPO 2011, 134), the Enlarged Board was concerned with the interpretation of the exclusion of surgical methods. In particular it considered and explained a *dictum* contained in opinion G 1/04 (*supra*, point 6.2.1 of the reasons) according to which "*methods of surgery within the meaning of*

Article 52(4) EPC [1973] include any physical interventions on the human or animal body in which maintaining the life and health of the subject is of paramount importance". The Enlarged Board found that this dictum was not meant to give an exhaustive definition of the term "methods of treatment by surgery" and to limit the exclusion to therapeutic surgery and continued as follows:

"On the contrary, the definition fits in very well with the previously established jurisprudence, decisions T 182/90 and 35/99, having held that the term surgical treatment embraces those interventions which, whatever their specific purpose, give priority to maintaining life and health of the human or animal body on which they are performed (T 35/99, loc.cit., point 4.1 of the Reasons), but that **in view of the purpose of the exclusion to lay down a separate medical sphere, it cannot be so broadly construed as to include destructive treatments, i.e. such procedures whose conscious (deliberate or incidental) end result is the death of living being 'under treatment'** (T 182/90, loc.cit., point 2.5.2 of the Reasons, T 35/99, loc.cit., points 3 et seq. of the Reasons). Such procedures do not qualify as methods in which maintaining the life and health of the subject is of paramount importance." (emphasis added by the board).

32. In view of the above considerations, the board is satisfied that the claimed methods are not excluded by Article 53(c) EPC.



*Conclusion*

33. The subject-matter of the claims of appellant's main request complies with the requirements of the EPC.

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to grant a patent on the basis of claims 1 to 27 of the appellant's request filed with letter dated 27 September 2011 and a description and figures to be adapted thereto.

The Registrar

The Chair

B. Atienza Vivancos

R. Gramaglia