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Datasheet for the decision of 23 July 2015

Case Number: T 0257/12 - 3.2.02

Application Number: 01989794.1

Publication Number: 1349490

IPC: A61B5/00, A61B6/00, G01N21/00

Language of the proceedings: EN

Title of invention:
FLUORESCENCE-MEDIATED MOLECULAR TOMOGRAPHY

Patent Proprietor:
The General Hospital Corporation

Opponent:
Commissariat à l'Energie Atomique

Headword:

Relevant legal provisions:
EPC Art. 100(c), 123(2)

Keyword:
Added subject-matter (yes) - all requests

Decisions cited:

Catchword:

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Case Number: T 0257/12 - 3.2.02

D E C I S I O N
of Technical Board of Appeal 3.2.02
of 23 July 2015

Appellant: (Patent Proprietor)	The General Hospital Corporation 55 Fruit Street Boston, MA 02114 (US)
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Respondent: (Opponent)	Commissariat à l'Energie Atomique 25 Rue Leblanc Bâtiment "Le Ponant D" 75015 Paris (FR)
Representative:	Augarde, Eric Brevalex 56 Boulevard de l'Embouchure, Bât. B B.P. 27519 31075 Toulouse Cedex 2 (FR)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 12 December 2011 revoking European patent No. 1349490 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	E. Dufrasne
Members:	M. Stern
	C. Körber

Summary of Facts and Submissions

I. The proprietor lodged an appeal against the decision of the Opposition Division dispatched on 12 December 2011 revoking European patent No. 1 349 490.

II. The Opposition Division revoked the patent under Articles 100(c) and 123(2) EPC, finding that the subject-matter of independent method claim 35 of the patent as granted and of claim 1 of auxiliary requests I to VI filed with letter dated 28 October 2011 extended beyond the content of the original application

D0: WO-A-02/41 760.

III. Notice of appeal was filed by the patent proprietor on 8 February 2012 and the fee for appeal was paid on the same day. A statement setting out the grounds of appeal was received on 12 April 2012.

IV. Oral proceedings were held on 23 July 2015.

The appellant (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained as granted or, in the alternative, on the basis of one of the auxiliary requests I to VI, all filed with letter dated 28 October 2011.

The respondent (opponent) requested that the appeal be dismissed.

V. Independent claim 35 of the granted patent (**main request**) reads as follows:

"35. A method of obtaining a three-dimensional, quantitative, molecular tomographic image of a target region within an object, the method comprising
directing excitation light from multiple points into the object;
detecting excitation light transmitted through the object;
detecting fluorescent light emitted from multiple points from the object by at least one fluorescent molecule; and
processing the detected excitation light and fluorescent light to provide a three-dimensional tomographic image that corresponds to a three-dimensional target region within the object."

Independent claim 1 of the **auxiliary requests** reads as follows:

Auxiliary request I:

"1. A method of obtaining a three-dimensional quantitative, molecular tomographic image of a target region within an animal or human patient, the method comprising
directing near-infrared excitation light having a wavelength ranging from 550 to 950 nanometers from multiple points into the animal or human patient;
detecting excitation light transmitted through the animal or human patient;
detecting fluorescent light emitted from multiple points from the animal or human patient by at least one fluorescent molecule; and
processing the detected excitation light and fluorescent light to provide a three-dimensional tomographic image that corresponds to a three-

dimensional target region within the animal or human patient."

Auxiliary request II:

"1. A method of obtaining a three-dimensional quantitative, molecular tomographic image of a target region within an animal or human patient using transillumination of the target region at multiple projections, the method comprising
directing near-infrared excitation light having a wavelength ranging from 550 to 950 nanometers from multiple points into the animal or human patient;
detecting excitation light transmitted through the animal or human patient;
detecting fluorescent light emitted from multiple points from the animal or human patient by at least one fluorescent molecule; and
processing the detected excitation light and fluorescent light to provide a three-dimensional tomographic image that corresponds to a three-dimensional target region within the animal or human patient."

Auxiliary request III:

"1. A method of obtaining a three-dimensional quantitative, molecular tomographic image of a target region within an animal or human patient using transillumination of the target region at multiple projections, the method comprising
administering a near-infrared fluorescent molecular probe to the animal or human patient, wherein the molecular probe selectively accumulates within a target region in the animal or human patient;

directing near-infrared excitation light having a wavelength ranging from 550 to 950 nanometers from multiple points into the animal or human patient;
detecting excitation light transmitted through the animal or human patient;
detecting fluorescent light emitted from multiple points from the animal or human patient by at least one fluorescent molecule; and
processing the detected excitation light and fluorescent light to provide a three-dimensional tomographic image that corresponds to a three-dimensional target region within the animal or human patient and to the quantity of molecular probe accumulated in the target region."

Auxiliary request IV:

"1. A method of obtaining a three-dimensional quantitative, molecular tomographic image of a target region within an animal or human patient using transillumination of the target region at multiple projections and segmenting the target region volume into a number of discrete voxels, the method comprising administering a near-infrared fluorescent molecular probe to the animal or human patient, wherein the molecular probe selectively accumulates within a target region in the animal or human patient;
directing near-infrared excitation light having a wavelength ranging from 550 to 950 nanometers from multiple points into the animal or human patient;
detecting excitation light transmitted through the animal or human patient;
detecting fluorescent light emitted from multiple points from the animal or human patient by at least one fluorescent molecule; and

processing the detected excitation light and fluorescent light to provide a three-dimensional tomographic image that corresponds to a three-dimensional target region within the animal or human patient and to the quantity of molecular probe accumulated in the target region."

Auxiliary request V:

"1. A method of obtaining a three-dimensional quantitative, molecular tomographic image of a target region within an animal or human patient using transillumination of the target region at multiple projections, the method comprising
administering a near-infrared fluorescent molecular probe to the animal or human patient, wherein the molecular probe selectively accumulates within a target region in the animal or human patient;
directing near-infrared excitation light having a wavelength ranging from 550 to 950 nanometers from multiple points into the animal or human patient;
detecting excitation light transmitted through the animal or human patient without a fluorescence filter to acquire an intrinsic signal from the animal or human patient at each wavelength;
detecting fluorescent light emitted from multiple points from the animal or human patient by the fluorescent molecular probe with the fluorescence filter on, so that only the fluorescent emission wavelength is collected; and
processing the detected excitation light and fluorescent light to provide a three-dimensional tomographic image that corresponds to a three-dimensional target region within the animal or human patient and to the quantity of molecular probe accumulated in the target region."

Auxiliary request VI:

"1. A method of obtaining a three-dimensional quantitative, molecular tomographic image of a target region within an animal or human patient using transillumination of the target region at multiple projections, the method comprising
administering a near-infrared fluorescent molecular probe to the animal or human patient, wherein the molecular probe selectively accumulates within a target region in the animal or human patient;
directing near-infrared excitation light having a wavelength ranging from 550 to 950 nanometers from multiple points into the animal or human patient;
detecting excitation light transmitted through the animal or human patient without a fluorescence filter to acquire an intrinsic signal from the animal or human patient at each wavelength;
detecting fluorescent light emitted from multiple points from the animal or human patient by the fluorescent molecular probe with the fluorescence filter on, so that only the fluorescent emission wavelength is collected;
detecting intrinsic light which passed through the fluorescent filter with removed animal or human patient; and
processing the detected light to provide a three-dimensional tomographic image that corresponds to a three-dimensional target region within the animal or human patient and to the quantity of molecular probe accumulated in the target region."

VI. The arguments of the appellant (patent proprietor) relevant for the present decision are summarised as follows:

A basis for claim 35 of the patent was given by the combination of claims 30 and 33 of the original application. Claim 30 defined the processing of the detected fluorescent light (M1) to provide a three-dimensional image. Claim 33 explained that the fluorescent (M1) and intrinsic (M2) signal measurements were used in the processing step. Claim 33 did not include any specific formula and did not include signals M3 to M5, M3 being a signal due to fluorescence background and/or high pass filter imperfections, M4 being a signal from intrinsic background ambient light and from noise of the CCD detector, and M5 being a background-medium diffuse signal. The original application disclosed using measurements M1 and M2 without having to measure M3 to M5.

The parameters M3 to M5 were optional. Page 34, lines 30 to 31 described an example in which only a subset of parameters M1 to M4 was used, but no M5. On page 4, lines 26 to 29 it was explained that M3 could be calculated based on M2. Looking at the formula $M = (M1 - M3)/(M2 - M4)$ on page 28, line 11, it was unambiguously clear to the skilled person that M4 could be neglected because it was a background noise signal which was small compared to the intrinsic signal M2 (page 4, lines 7 to 11). Thus, it was immediately clear to the skilled person that M3 to M5 were not essential, neither to the invention nor to the detailed embodiment described on pages 27 and 28. Furthermore, the application made it clear that there were several ways to calibrate the measurements (page 28, line 22 and page 4, lines 8 to 13). Hence, only the measurements M1 (fluorescence signal) and M2 (intrinsic signal) were essential for obtaining tomographic images. The measurements M3, M4 and M5 were clearly not as

important as M1 and M2. M3 to M5 were not necessary in the event of good filters, enclosures and CCDs and only represented a further improvement which was, however, not required under certain circumstances. Self-calibration was not essential since the sentence on page 8, lines 7 to 10 indicated that pre-calibration could be absent and since it was not mentioned in some of the examples presented on page 3, line 27 to page 4, line 6.

Accordingly, claim 35 of the main request was in line with Article 123(2) EPC.

The arguments presented regarding patent claim 35 applied mutatis mutandis to claim 1 of the auxiliary requests as well. Therefore, the auxiliary requests were also in line with Article 123(2) EPC.

VII. The arguments of the respondent (opponent) relevant for the present decision are summarised as follows:

The method of claim 35 of the patent extended beyond the content of the application as filed (Articles 100(c) and 123(2) EPC). In particular, there was no basis for obtaining a three-dimensional tomographic image by processing the detected excitation light (M2) and fluorescent light (M1). The combination of original claims 30 and 33 provided no basis, because original claim 33 defined self-calibrating the (fluorescent) digital signal by combining the fluorescent (M1) and the intrinsic signal measurements from the patient (M2) and the background measurements (M3, M4, M5) to obtain a three-dimensional image. Patent claim 35 failed to define the step of self-calibration, in particular using the background measurements M3, M4 and M5. The formulation of original

claim 33 showed that the background measurements (M3, M4 and M5) and the method step of self-calibration were essential.

The objection under Article 123(2) EPC applied as well to claim 1 of the auxiliary requests.

Reasons for the Decision

1. The appeal is admissible.

2. The original application (D0) deals with fluorescence-mediated tomography, which involves obtaining measurements of light at multiple projections through a turbid medium such as tissue, and using these measurements to obtain a three-dimensional image of the medium via tomographic analysis (page 15, lines 15 to 25). For this, in general, a light source (e.g. a near-infrared or visible light source) provides incident light which is directed at multiple points into an object, e.g. an animal or human patient, a detection array collects the fluorescent light emitted from the object, and a processor processes the digital signal produced by the detector to provide an image on an output device (page 3, lines 11 to 26).

3. According to independent method claim 35 of the granted patent, excitation light (M2) transmitted through the object and fluorescent light (M1) emitted from the object is detected and then processed to provide a three-dimensional tomographic image. In the description of the original application, D0, the detection of the excitation light transmitted through the object is referred to as M2 (denominated "intrinsic signal") and

the detection of the fluorescent light is referred to as M1 (page 27, lines 2 to 7).

4. The appellant-proprietor considered that the method of claim 35 of the patent was properly based on the combination of original claims 30 and 33. The Board, however, disagrees for the reasons given hereinafter.

5. Original independent claim 30 defines the processing of the detected fluorescent light (M1) to provide a three-dimensional image. It is true that original dependent claim 33 defines that the fluorescent (M1) and the intrinsic (M2) signal measurements are used in the processing step. However, the processing according to original claim 33 goes further in that it also defines the step of **self-calibrating** the (fluorescent) digital signal by combining fluorescent (M1) and intrinsic (M2) signal measurements from the patient **and background medium** to obtain a three-dimensional image. Examples of such background signals which affect the fluorescent signal (M2) are presented in the description and in Figure 5 as M3, M4 and M5. In particular, M3 is a signal due to fluorescence background and/or high pass filter imperfections (page 27, lines 10 to 12; page 4, lines 10 to 11); M4 is a signal from intrinsic background ambient light (page 4, line 11) and from noise of the CCD detector (page 27, lines 27 to 28; page 28, lines 2 to 3); M5 is a background-medium diffuse signal (page 27, lines 28 to 30; page 4, line 13).

6. Insofar as patent claim 35 fails to define the aforementioned step of self-calibration taking into account in particular background signals, it generalises the method of original claims 30 and 33.

The Board considers that this generalisation is not allowable in view of the teaching of D0 as a whole.

6.1 Throughout the description it is disclosed that the image is obtained from measurements which are presented as a function of the measurements of fluorescence (M1) and of an intrinsic signal (M2) corrected for background noise (page 4, lines 1 to 2; page 4, lines 8 to 9; page 6, lines 15 to 17). In the detailed embodiment presented on page 28, lines 7 to 25, the measurements of fluorescence (M) and intrinsic signal (M') are self-calibrated by using the functions

$$M = (M1 - M3)/(M2 - M4) \text{ and}$$
$$M' = \log(M2 - M4)/(M5 - M4).$$

According to the flow chart of Figure 5 and as described on page 26, lines 25 to 31, five sets of measurements M1 to M5 are obtained. According to circumstances, subsets of these measurements are used. For example, the parameter M3 may be calculated from M2 (page 4, lines 26 to 29); consideration of M5 may even be dispensed with (page 34, lines 30 to 31). However, in all the examples disclosed the measurement M4 (reflecting background noise and CCD detector noise) is used. There is thus no disclosure in D0 that M4 may be optional. That the noise signal M4 may be smaller than the intrinsic signal M2 and could hence be neglected, as argued by the appellant-proprietor, relates to conclusions which the skilled person may possibly draw from D0 upon reflection. This is, however, not subject-matter which is directly and unambiguously derivable from D0, which is the decisive criterion when assessing the admissibility of amendments (Case Law of the Boards of Appeal of the EPO, II.E.1.7.1, 7th edition 2013).

Moreover, the fact mentioned by the appellant-proprietor that D0 disclosed that other functions, different from M and M', could be envisioned to self-calibrate the fluorescent and intrinsic signal measurements (page 4, lines 8 to 13; page 28, lines 21 to 27) certainly does not amount to any specific disclosure of these other self-calibration functions. On the contrary, these passages emphasise that self-calibration is a necessary requirement.

6.2 The need for self-calibration for image reconstruction is prominently highlighted in the first paragraph of the "Summary" on page 3 of D0. Moreover, in each of the examples presented in the paragraph bridging pages 3 and 4, the processing of the detected digital signals includes corrections taking into account background signals or self-calibrations. In view of this teaching, the sentence on page 8, lines 7 to 10 is to be understood as underlining the possibility of carrying out the imaging of an object without the need for any additional prior calibration. In no embodiment presented in D0 is the processing of the detected fluorescent and the intrinsic signals performed without a self-calibration including at least one of the background signals M3, M4 and M5. Hence, the appellant-proprietor's argument that M3, M4 and M5 "are optional" is not considered to be founded.

6.3 The appellant-proprietor also argued that the application clearly and unambiguously disclosed that only measurements M1 and M2 were "essential" and that M3 to M5 were "not essential". The appellant-proprietor failed to say, however, in which way, or for what purpose, it assumed the latter measurements to be "not essential".

In the absence of such indication, the assertion is not comprehensible. It may be assumed that this argument was equivalent to another argument presented, i.e. that the measurements M3, M4 and M5 were "clearly not as important as M1 and M2". Whilst the "importance" of measurements is a likewise ambiguous and ill-defined aspect, the generalisation of the subject-matter of original claim 33 does not become allowable (only) because the eliminated features are deemed to be "less important".

7. The Board thus concludes that the subject-matter of claim 35 of the granted patent extends beyond the content of the application as filed, contrary to Article 123(2) EPC. As a consequence, the ground for opposition under Article 100(c) EPC prejudices the maintenance of the patent.

8. Whilst the respondent-opponent objected that, for the aforementioned reasons, claim 1 of auxiliary requests I to VI also contained added subject-matter, the appellant-proprietor only indicated in its statement of the grounds of appeal that its arguments presented regarding patent claim 35 applied mutatis mutandis to the auxiliary requests as well. At the oral proceedings, the appellant-proprietor just referred to its written submissions in the last two paragraphs of the statement of grounds of appeal.

The Board therefore concludes that claim 1 of auxiliary requests I to VI, none of which comprises the step of self-calibration taking into account background signals, contravenes Article 123(2) EPC for the aforementioned reasons.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

D. Hampe E. Dufrasne

Decision electronically authenticated