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Datasheet for the decision of 25 June 2019

Case Number: T 0434/15 - 3.3.01

Application Number: 02750370.5

Publication Number: 1411918

IPC: A61K31/33, A61K31/555, A61K38/19, A61P43/00

Language of the proceedings: EN

Title of invention:
METHODS TO MOBILIZE PROGENITOR/STEM CELLS

Patent Proprietor:
Genzyme Corporation

Opponents:
Generics [UK] Limited (trading as Mylan)
Taylor Wessing LLP
Actavis Group PTC ehf

Headword:
Plerixafor/GENZYME

Relevant legal provisions:
EPC Art. 123(2), 53(c)

Keyword:
Main request: amendments - allowable (no)
Auxiliary request 1: exceptions to patentability - method for treatment by surgery

Decisions cited:
G 0001/07

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Case Number: T 0434/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 25 June 2019

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 February 2015 concerning maintenance of the European Patent No. 1411918 in amended form**

Composition of the Board:

Chairman A. Lindner
Members: M. Pregetter
T. Sommerfeld
M. Blasi
L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 411 918 is based on European patent application No. 02750370.5. The application had been filed as an international application published as WO 2003/011277 (hereinafter "application as filed").

II. The following documents, cited during the opposition and appeal proceedings, are referred to herein:

(12) Gazitt, J Hematother. Stem Cell Res. 2001, 10, 229-236

(16) Olavarria et al., Curr Opin Hematol, 2000, 7, 191-196

(17) Croop et al., Bone Marrow Trans, 2000, 26, 1271-1279

(18) Declaration of Prof. Charles F. Craddock, 5 pages, and exhibits, 25 pages

(36) Aiuti et al., J Exp Med, 1997, 185(1), 111-120

III. Independent claims 1 and 9 of the patent as granted read as follows:

"1. A method to obtain progenitor and/or stem cells from a subject, which method comprises
(a) administering to said subject an amount of a compound sufficient to mobilize said progenitor and/or stem cells into the peripheral blood of said subject, followed by
(b) harvesting said progenitor and/or stem cells,

wherein said compound is 1,1'-[1,4-phenylene-bis-

(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane or a pharmaceutically acceptable salt or metal complex thereof."

"9. A compound for use in a method to treat a hematopoietic deficit in a subject, wherein said method comprises
(a) administering to said subject an amount of a compound sufficient to mobilize progenitor and/or stem cells into the peripheral blood of said subject,
(b) harvesting said progenitor and/or stem cells, and
(c) transplanting said progenitor and/or stem cells to said subject,

wherein said compound is 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane or a pharmaceutically acceptable salt or metal complex thereof."

IV. Three oppositions were filed against the granted patent. By an interlocutory decision, the opposition division found that the then auxiliary request 11 (set of claims filed on 7 August 2014 together with a description adapted during oral proceedings before the opposition division and the figure from the patent specification) met the requirements of the EPC.

The opposition division further found that claims 1 to 8 of the main request (patent as granted) met the requirements under Article 123(2) EPC. The main request did not fulfil the requirements of Article 53(c) EPC since claim 1 of said request defined a method for treatment by therapy and, as it included a surgical step, was also directed to a method for treatment by surgery. The same findings concerning Article 53(c) EPC were made for auxiliary requests 1 to 7; objections

were raised against auxiliary request 8 only for the presence of a method of therapy. Claim 1 of auxiliary request 9 and claim 1 of auxiliary request 10 were found to contravene the requirements of Article 123(2) EPC.

V. The patent proprietor and the three opponents each filed an appeal against the decision of the opposition division. In the following, the four appellants will be identified by their role in the opposition proceedings.

VI. Oral proceedings before the board took place on 25 June 2019, in the absence of opponent 2, who had been duly summoned but did not attend.

VII. During the oral proceedings the patent proprietor filed a set of claims of a new auxiliary request 1, replacing all auxiliary requests then on file and consisting of claims 1 to 8 of the patent as granted.

VIII. The patent proprietor's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Amendments

The basis for claim 9 of the patent as granted came from the general passages of the description and in particular paragraph [0012] of the application as filed, in combination with common general knowledge. The application as filed aimed at the mobilisation of progenitor/stem cells in subjects by administration of a certain drug (paragraph [0002]). In paragraph [0015] the use of these mobilised progenitor and/or stem cells in cell transplantation, after having been harvested, was presented as one of the key methods in which the

progenitor/stem cells could be used. It was clear from paragraph [0012] that mobilised stem cells of the prior art, especially CD34+ cells, were to be used in autologous stem cell transplantation. Example 3 disclosed that the novel and inventive mobilisation method led to the obtention of CD34+ cells (paragraph [0057]). The autologous stem cell transplantation described in paragraph [0012] represented the key clinical use for mobilised and harvested progenitor/ stem cells. This was common general knowledge as could be seen from documents (12), (16), (17) and (36). Paragraph [0012] thus provided direct and unambiguous disclosure that one of the uses of mobilised progenitor/stem cells was autologous transplantation. The application as filed thus provided a basis for claim 9 of the main request.

Admission of auxiliary request 1

The claims of auxiliary request 1 corresponded to claims 1 to 8 of the patent as granted. Thus, no new situation arose.

Article 53(c) EPC - surgery

Apheresis represented a safe, routine technique within the meaning of decision G 1/07 of the Enlarged Board of Appeal (see reasons 3.4.2.2). According to document (18), apheresis procedures for harvesting progenitor and/or stem cells were not considered surgical in today's technical reality. Furthermore, apheresis neither represented the core of the medical profession's activities nor did it involve a substantial health risk. No method of surgery was thus claimed.

IX. The opponents' arguments, including those made in writing by opponent 2 and insofar as they are relevant to the present decision, may be summarised as follows:

Amendments

While the application as filed referred several times to cell transplantation in general, there was no reference to autologous stem cell transplantation in combination with the drug, the specific steps (a) to (c), or a patient having any kind of haematopoietic deficit. Paragraph [0012] of the application as filed merely discussed a number of scientific papers as background art and therefore could not serve as a basis for the subject-matter of claim 9 as granted. Autologous stem cell transplantation was disclosed in the application as filed only for *ex vivo* methods. Concerning the reference to common general knowledge of stem cell transplantation, it was to be noted that the documents cited and paragraph [0012] of the application as filed related to methods including a step of inducing a haematopoietic deficit by chemotherapy and/or radiation therapy. Such a step was absent from claim 9 as granted. Neither paragraph [0012] nor any other passage of the application as filed provided a basis for claim 9 as granted.

Admission of auxiliary request 1

The admission of auxiliary request 1 was at the board's discretion.

Article 53(c) EPC - surgery

Claim 6 of auxiliary request 1 defined apheresis, which was a treatment of the human body by surgery. The

process of apheresis involved the removal of whole blood from the human body, the separation and collection of certain components of the human blood and retransfusion of the remaining blood components into the human body. Such a method constituted a substantial physical intervention, required the presence of a medical expert and potentially led to long term effects for the patient. It thus involved significant health risks. It was furthermore to be stressed that in the present case the apheresis was to be carried out on very ill patients. There was thus no doubt that apheresis was a method of surgery.

X. The parties' final requests were as follows:

Appellant I (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained as granted, i.e. that the oppositions be rejected (main request), or alternatively, that the patent be maintained in amended form on the basis of the set of claims of auxiliary request 1 as filed during the oral proceedings.

Appellants II and IV (opponents 1 and 3, respectively) requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Appellant III (opponent 2) requested in writing that the decision under appeal be set aside and that the patent be revoked in its entirety.

Reasons for the Decision

1. The appeals are admissible.

2. The oral proceedings before the board took place in the absence of opponent 2, who had been duly summoned but had chosen not to attend. According to Rule 115(2) EPC and Article 15(3) RPBA, the board was not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case. Hence, the board was in a position to announce a decision at the conclusion of the oral proceedings, as provided for by Article 15(6) RPBA.

3. *Main request - amendments (Article 100(c) EPC)*

3.1 Claim 9 of the main request defines a compound for use in a method to treat a haematopoietic deficit in a subject. The method comprises three method steps. Step (a) defines the administration of the compound. Step (b) relates to the harvesting of progenitor and/or stem cells from the subject to whom the compound was administered. Finally, step (c) requires that the harvested progenitor and/or stem cells are transplanted into this subject.

The progenitor/stem cells under consideration are thus autologous cells of the subject to be treated. The claim defines neither a time line, i.e. any indication of the periods of time that may or must elapse between steps (a), (b) and (c), nor any indication of when and how the haematopoietic deficit arises.

3.2 The wording of the claim thus does not define autologous stem cell transplantation encompassing a step of inducing a (severe) haematopoietic deficit by intensive chemotherapy or myeloablative therapy, including radiotherapy, after harvesting and before

implantation, i.e. between steps (b) and (c).

However, the passage in paragraph [0012] of the description as filed (see WO 2003/011277) and the common general knowledge, as ascertained from documents (12), (16), (36) and (17), invoked by the patent proprietor as the basis for the subject-matter of claim 9, relate only to this form of autologous stem cell transplantation.

Paragraph [0012] states that: "Recently, considerable attention has been focused on the number of CD34+ cells mobilized in the pool of peripheral blood progenitor cells used for autologous stem cell transplantation. The CD34+ population is the component thought to be primarily responsible for the improved recovery time after chemotherapy and the cells most likely responsible for long-term engraftment and restoration of hematopoiesis." It is clear from this passage that the autologous stem cells are to be implanted after chemotherapy for restoration of haematopoiesis.

Document (12) starts its introduction with the statement that autologous, mobilised, peripheral blood stem cells provide a rapid and sustained haematopoietic recovery after the administration of high-dose chemotherapy or chemoradiotherapy in patients with haematological malignancies (page 229, left-hand column, lines 1 to 8). Autologous stem cell transplantation is thus clearly linked to a method specifying induction of a haematopoietic deficit by chemo- or chemoradiotherapy.

Document (16), page 191, right-hand column, second paragraph, states that peripheral blood progenitor cell support has replaced bone marrow transplantation in the

treatment of chemosensitive malignancies. It is apparent from the "Conclusions" on page 195, left-hand column, that autologous peripheral blood progenitor cells are to be used "as stem cell support for high-dose chemotherapy", so again only in the context of a haematopoietic deficit caused by chemotherapy.

Document (17) describes that collecting mobilised peripheral blood progenitor cells has become the accepted method for obtaining cells for autologous stem cell support during intensive chemotherapy as well as for autologous transplantation after myeloablative therapy (page 1271, first paragraph after summary). Autologous transplantation is thus clearly linked to myeloablative therapy.

Document (36) explains mechanisms for mobilising CD34+ haematopoietic progenitor cells and refers to autologous and allogeneic transplantation, though without indicating any steps (page 117, right-hand column, last paragraph, lines 2 to 4).

Consequently, the disclosure of paragraph [0012], read on its own or with the common general knowledge in mind, cannot provide the basis for claim 9, which defines steps (a) to (c) but does not define a step of inducing a haematopoietic deficit. The subject-matter of claim 9 of the main request is thus not directly and unambiguously disclosed in the application as filed.

Having come to this conclusion, it is not necessary to further consider whether paragraph [0012], which is found in a part of the description which deals with the background art, may act as a basis for amendments.

3.3 Apart from paragraph [0012] of the description as filed, the board considered the following further passages:

- Paragraph [0015] describes treatment methods on which the application is based. It is clearly stated that the progenitor and/or stem cells which have been mobilised by the compound under consideration (AMD3100) may be harvested and used in cell transplantation.
- Paragraph [0017] points to the fact that the methods of the invention also include treatment of cell populations *ex vivo* with AMD3100.
- A generic reference to stem cell transplantations can be found in the two last sentences of paragraph [0023].
- Paragraph [0043] mentions *ex vivo* treatment protocols, referring to autologous cells in this context.
- Finally, paragraph [0045], last sentence, makes a further, general reference to stem cell transplantation.

None of these passages refers directly and unambiguously to autologous stem cell transplantation by a method having steps (a) to (c) as defined in claim 9. The generic reference to "stem cell transplantation" cannot serve as a basis for the subject-matter of claim 9. Apart from the fact that stem cell transplantation can be carried out with autologous or allogeneic cells, it is obvious, e.g. from paragraphs [0017] and [0043], that treatment protocols are not limited to *in vivo* mobilisation, but may include treatments that are carried out *ex vivo*. The generic reference to stem cell transplantation thus has to be seen as a reference to an indeterminate number of different treatment protocols, which does not correspond directly and unambiguously to steps (a) to

(c) of claim 9 of the main request.

3.4 All parties agreed that the claims of the application as filed do not provide a basis for claim 9 of the main request.

3.5 Having found no basis for steps (a) to (c), which do not include a step of inducing a haematopoietic deficit by chemotherapy or radiotherapy, in combination with autologous progenitor and/or stem cells (i.e. cells of "said subject"), it is not necessary to establish whether there is a basis for a haematopoietic deficit not arising from chemo- or radiation therapy.

The subject-matter of claim 9 of the main request extends beyond the content of the application as filed and therefore the ground for opposition under Article 100(c) EPC prejudices the maintenance of the patent as granted.

4. *Auxiliary request 1*

4.1 *Admission (Article 13 RPBA)*

Claims 1 to 8 of auxiliary request 1 are identical to claims 1 to 8 of the patent as granted. The deletion of claims 9 to 18 did not lead to a situation in which any new issues would have had to be addressed. Consequently, the board decided to admit auxiliary request 1 into the proceedings.

4.2 *Methods for treatment by surgery (Article 53(c) EPC)*

4.2.1 The following reasoning applies to methods according to claims 1 and 6, i.e. methods in which the progenitor/

stem cells are harvested by apheresis.

4.2.2 Decision G 1/07 of the Enlarged Board of Appeal (see OJ EPO 2011, 134) has established a certain direction for the consideration of whether certain method steps are to be considered as methods of treatment of the human body by surgery. The exclusion of such methods from patentability should be justified on grounds of public health, the protection of patients and the freedom of the medical profession to apply the treatment of choice to its patients (see G 1/07, reasons, point 3.4.2.4, third paragraph).

4.2.3 The issue of protection of patients is tied to the health risk linked to the method under consideration.

Apheresis is a method in which blood is removed from a person, passed through an apparatus for separating and collecting a particular constituent of the blood (in the present case, stem/progenitor cells) and re-transfused without the collected constituent.

For the steps of removing and returning blood, cannulas are inserted into the person's veins. Depending on the vein chosen, different flow rates may be expected (see document (18), points 11 and 15). During the treatment, changes in blood volume occur (document (18), point 14), which might necessitate fluid replacement to keep the correct intravascular volume. The types of fluid used for replacement and the side effects/risks linked to this selection have not been discussed. The removed blood undergoes a separation step in the apheresis machine, where the stem/progenitor cells are removed. The method of apheresis thus includes a step in which blood, an important organ of the human body, is manipulated. The stem/progenitor

cells which are removed play an important role in haematopoiesis. According to document (18), point 5, all mature blood cells such as leucocytes, erythrocytes and thrombocytes, i.e. cells that are indispensable for oxygen transport, immune response and injury management, are formed from these stem/progenitor cells. Apheresis thus has to be carried out with extreme care to avoid damage to the remaining blood and to the stem/progenitor cells that are removed for further use.

In addition to the health risks linked to the steps of removing and returning blood and any necessary fluid replacement, there are health risks linked to the handling of the manipulated blood, which is immediately returned to the person, and to the handling of the cells that are removed. Consequently, apheresis is a substantial physical intervention involving considerable health risks.

4.2.4 The patent proprietor has pointed to reasons 3.4.2.2 of G 1/07. In paragraph 5 of this point of the reasons, the Enlarged Board of Appeal states that excluding from patentability also such methods as make use of in principle safe routine techniques, even when of invasive nature, appears to go beyond the purpose of the exclusion of treatments by surgery from patentability in the interest of public health.

In his declaration (document (18)), Prof. Craddock claimed that he had the responsibility for the treatment and management of patients with haematological malignancies. He further pointed to the fact that he himself was not involved in the actual processes necessary to carry out the apheresis. These process steps were carried out by nursing staff

(point 13). The Queen Elizabeth Hospital, where Prof. Craddock was based, performed about 200 apheresis sessions a year. It was the second largest centre in the UK performing adult stem cell transplantation.

However, the fact that a certain method is routine for a highly specialised centre cannot automatically lead to the conclusion that such a method would generally be a safe and routine technique.

4.2.5 Apheresis is thus a method using invasive techniques that allow for extra corporeal manipulation of an organ of the human body. There are considerable health risks involved. Furthermore, apheresis cannot be considered to be a generally safe, simple, routine procedure. Consequently, apheresis has to be seen as a method of surgery within the meaning of Article 53(c) EPC.

4.2.6 Having come to the conclusion that the step of harvesting, when carried out by apheresis, includes a method of surgery, it is not necessary to assess whether or not the claimed method is a method of therapy.

4.2.7 The subject-matter of claim 1 of auxiliary request 1 encompasses a method for treatment of the human body by surgery and is thus not allowable (Article 53(c) EPC).

5. Thus, neither the main request nor auxiliary request 1 meets the requirements of the EPC. Consequently, the patent is to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated