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Datasheet for the decision of 2 March 2010

Case Number: T 1667/07 - 3.3.08

Application Number: 97907592.6

Publication Number: 0914415

IPC: C12N 5/08

Language of the proceedings: EN

Title of invention:
Method and compositions for obtaining mature dendritic cells

Patentee:
THE ROCKEFELLER UNIVERSITY, et al

Opponent:
Dr. Kübler GmbH

Headword:
Dendritic cells/ROCKEFELLER UNIVERSITY

Relevant legal provisions:
RPBA Art. 12, 13

Relevant legal provisions (EPC 1973):
EPC Art. 56, 100(a), 100(b), 113, 114(1), 114(2)
EPC R. 55(c)

Keyword:
"Fresh grounds for opposition - disregarded"
"Documents E11, E12, E13 - disregarded"
"Claims as granted - sufficiency of disclosure - yes"
"Inventive step - yes"

Decisions cited:
G 0009/91, G 0010/91, G 0001/99

Catchword:
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Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1667/07 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 2 March 2010

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted on 10 May 2007 rejecting the opposition filed against European patent No. 0914415 pursuant to Article 102(2) EPC 1973.

Composition of the Board:

Chairman:	L. Galligani
Members:	M. R. Vega Laso
	C. Heath

Summary of Facts and Submissions

I. European patent No. 0 914 415 with the title "Method and compositions for obtaining mature dendritic cells" was granted on European patent application No. 97 907 592.6 (published as WO 97/29182) which had been filed as PCT/US97/02110 on 10 February 1997. The patent was granted with 18 claims.

II. Claims 1, 11 and 15 as granted read as follows:

"1. An *in vitro* method of producing stable mature CD83 positive dendritic cells from a population of CD14 positive and substantially CD83 negative pluripotential cells, wherein said pluripotential cells are capable of becoming macrophages or dendritic cells, said method comprising

(a) contacting the population of CD14 positive and substantially CD83 negative pluripotential cells with a differentiation composition comprising at least one cytokine which causes immature dendritic cells which are substantially CD14 negative and CD83 negative to develop from said population of pluripotential cells, wherein said cytokine is GM-CSF, or a combination of GM-CSF and either one or both of IL-4 and IL-13, and concurrently or subsequently

(b) contacting the immature dendritic cells with a dendritic cell maturation factor being a PBMC conditioned media or fixed *Staphylococcus aureus* (Pansorbin)®, for a time sufficient for said immature dendritic cells to mature into stable,

substantially CD14 negative, CD83 positive mature dendritic cells.

11. An assay to detect a dendritic cell maturation factor comprising:

(a) obtaining immature dendritic cells by culturing a population of pluripotent cells having the potential of expressing either macrophage or dendritic cell characteristics in a medium containing at least one cytokine, wherein said at least one cytokine is GM-CSF, or a combination of GM-CSF and either one or both of IL-4 and IL-13;
(b) contacting a test substance with the culture of immature dendritic cells to determine if the test substance is a dendritic cell maturation factor; and
(c) detecting the maturation of the immature dendritic cells in response to the presence of the test substance, wherein maturation is detected by detecting either one or more of 1) an increase expression of one or more of p55, CD83, CD40 or CD86 antigens; 2) a decrease in expression of CD115, CD14, CD32 or CD68 antigen; or reversion to a macrophage phenotype **characterized by** increased adhesion and loss of veils following the removal of cytokines which promote maturation of PBMCs to the immature dendritic cells.

15. The use of a dendritic cell maturation factor being a PBMC conditioned media for the preparation of a pharmaceutical composition for increasing the number of mature dendritic cells in an individual for activating T cells against antigens associated with disease."

Claims 2 to 6, which depend on claim 1, are directed to specific methods of producing stable mature dendritic cells. Independent claim 7 and dependent claims 8 to 10 concern methods of activating T cells which comprise the step of preparing stable mature dendritic cells according to the method of claims 1 to 6. Independent claim 12 and dependent claims 13 and 14 relate to culture media useful for obtaining stable, mature dendritic cells. Dependent claims 16 to 18 specify features which further characterise the use of PBMC as dendritic cell maturation factor according to claim 15.

III. The patent was opposed on the grounds for opposition under Article 100(a) and (b) EPC 1973. In the statement filed under Rule 55(c) EPC 1973, the opponent maintained that "*at least*" the subject-matter of claims 1 and 11 lacked an inventive step within the meaning of Article 56 EPC 1973, and that the invention defined in claims 1 and 11 was not disclosed in the patent in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. As evidence in support of the grounds for opposition documents E1 to E3 (see section XIII below) were submitted. In connection with the ground for opposition of Article 100(b) EPC 1973, the opponent pointed to observations under Article 115 EPC 1973 which had been presented by Prof. J.C. Huber during the examination of the application on which the present patent was granted. However, neither a copy of Prof. Huber's observations nor a copy of any of the 39 scientific articles to which reference was made therein was submitted.

IV. In a decision posted on 10 May 2007, the opposition division found that the invention claimed in claims 1, 11 and 15 was sufficiently disclosed in the patent, and that, having regard to document E1 as the closest prior art, the subject-matter of independent claims 1, 11 and 15 involved an inventive step. Consequently, the opposition division rejected the opposition under Article 102(2) EPC 1973.

V. The appellant (opponent) lodged an appeal against the decision of the opposition division. Together with the statement of grounds of appeal, the appellant filed additional documents E4 to E7 (see section XIII below) and copies of eleven scientific publications cited in documents E5 and E6. As support for its line of argument on lack of inventive step concerning the subject-matter of claims 1 to 14, the appellant relied on document E1 filed at the outset of the opposition proceedings and documents E4 to E7 submitted together with the statement of grounds of appeal. As regards the ground of opposition under Article 100(b) EPC 1973, the sole argument put forward by the appellant concerned the pharmaceutical use claimed in claim 15. In its view, the claimed use was not sufficiently disclosed in the patent because the disease condition to be treated was not specified in claim 15. Finally, the appellant requested oral proceedings if the board did not intend to set aside the decision under appeal and to revoke the patent.

VI. The proprietors (respondents) replied to the statement of grounds of appeal and requested, as a subsidiary request, that oral proceedings be held.

VII. The appellant requested to be allowed to file observations to the respondents' reply within a period of three months.

VIII. In a communication dated 10 March 2008, the board indicated that it was unable to see any reasons which justified a further submission at that stage of the proceedings, especially in view of the fact that neither amended claims nor additional evidence had been filed by the respondents. The board also drew attention to Articles 12(2) and 13 of the Rules of Procedure of the Boards of Appeal (RPBA) as in force from 13 December 2007 (OJ EPO 2007, 536), and indicated that it intended to send a communication under Article 15(1) RPBA together with the summons to oral proceedings and to give the parties the opportunity to file submissions in response.

IX. The parties were summoned to oral proceedings. In the communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached to the summons, the board commented on some of the issues to be discussed during the oral proceedings, in particular concerning the documentary evidence filed with the statement of grounds of appeal, and the objections raised under Article 100(a) in conjunction with Article 56 and Article 100(b) EPC 1973.

X. Both parties replied to the board's communication.

XI. In its reply dated 2 February 2010, the appellant raised fresh objections under Article 100(a) EPC 1973 in conjunction with Articles 52(2)a), 54 and 57 EPC 1973, and Article 100(c) EPC 1973, relying, ***inter alia***,

on additional documentary evidence (documents E8 to E13; see section XIII below). Moreover, several scientific articles were cited by the appellant, but copies thereof were not filed.

XII. At the oral proceedings, which were held on 2 March 2010, the chairman of the board summarised the relevant facts as appearing from the appeal file and, after briefly summarising the history of the case, drew the parties' attention to the Rules of Procedure of the Boards of Appeal (RPBA), in particular Articles 12 and 13 RPBA, and to the restrictions imposed on the board concerning fresh grounds of opposition/appeal and late-filed evidence.

The parties addressed the Board in this respect. The appellant indicated that it still wished to rely on the fresh grounds of opposition/appeal and evidence mentioned in its letter dated 2 February 2010. The respondents objected to the introduction of both the fresh grounds of opposition/appeal and the additional documents.

The oral proceedings were adjourned several times in order to allow the appellant to specify which objections it wanted to raise, based on which documents, and whether or not these documents were on file. The appellant filed a list of objections in connection with the documents relied upon (see copy attached to the Minutes of the Oral Proceedings, dated 2 March 2010). It also filed a copy of document E14 (see section XIII below). Further time was given to the appellant in order for the list to be completed.

The representative of the respondents was asked if he needed time to respond. He declined and, with reference to the list, objected to the introduction of the fresh attacks concerning either novelty (for all claims) maintaining that this had not been a ground of opposition in opposition proceedings, or sufficiency of disclosure other than in connection with claim 15, this being the only issue raised in the statement of grounds of appeal. The respondents also objected to the introduction of documents E8 to E10, on the grounds that these documents related to the attack concerning sufficiency of disclosure. As to inventive step, the respondents submitted that E11, E12 and E13 should not be admitted because they were irrelevant, and documents E5 and E6 should be disregarded as being internet printouts without any identifiable date of publication. There was no objection to admitting document E14 into the procedure.

The above issues were then discussed with the parties, which at the end of the discussion were asked whether they wished to add anything else prior to the board taking a decision on the scope of the appeal and the documents to be admitted into the proceedings. As this was not the case, the oral proceedings were adjourned for deliberation.

After resuming the oral proceedings, the board indicated that it was prepared to hear arguments on sufficiency of disclosure with respect to claim 15, and on inventive step. Further, documents E11, E12 and E13 were not admitted into the proceedings. The board indicated also that documents E5 and E6 had no

identifiable publication date. Document E14 was admitted into the proceedings.

Sufficiency of disclosure was discussed in relation to claim 15 in view of the fact that there was no indication as to which specific disease should be treated. After the discussion on this point, arguments on inventive step were heard. The appellant based its attack on inventive step firstly on the combination of document E1 with document E4. Subsequently, document E2 was used as the starting point. The respondents had no objection against arguments on inventive step being based on document E2, and the issue was thus discussed with the parties. The appellant made a further attack against inventive step based on document E14, from which - in its view - claim 1 of the patent in suit only differed in the reference to a non-inventive selection of certain cells as starting material. The respondents had no formal objections to this attack being introduced only at a late stage of the proceedings and replied thereto. As for the alleged lack of inventive step concerning the remaining claims, the appellant referred to the appeal brief and the submissions of 2 February 2010.

After the discussion, the chairman asked the parties whether they had any further submissions on sufficiency and/or inventive step. There were none. The oral proceedings were adjourned for deliberation. The chairman then indicated that none of the arguments and documents presented had convinced the board to set aside the decision under appeal.

Once the requests put in writing were confirmed as final requests, the chairman asked the parties whether they had any further requests and/or observations.

The appellant requested to be informed why Article 114 EPC 1973 was not applied by the board in a way that all observations of a party would be taken into account. The chairman explained that - as indicated in the first part of the oral proceedings - the procedures at issue were conducted in accordance with the RPBA and with the case law of the Enlarged Board of Appeal and of the Boards of Appeal.

The appellant was not satisfied with this explanation and stated that the board should apply the law, that is Article 114(1) EPC 1973 as stated, and that the case law as applied by the Boards of Appeal was inconsistent with that provision. The appellant therefore made clear that, in its view, no sufficient opportunity had been given to be heard with all those arguments that it wished to have presented, and requested a decision by the board that would take into account all grounds of opposition/appeal that had been raised, as well as all arguments and documents presented during the entire procedure from examination up to the submissions made on 2 February 2010. After all, the patent was a right effective *erga omnes* and not just *inter partes*. Otherwise, the appellant felt that the right to be heard had been violated.

The respondents requested to reject such request.

The oral proceedings were adjourned on the appellant's request.

After resumption, the parties did not wish to make any additional submissions. The chairman then closed the debate and announced the decision.

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

E1: R. Steinman et al., The Journal of Investigative Dermatology, July 1995, Vol. 105, No. 1, Supplement, pages 2S to 6S;

E2: EP 0 584 715 B1, application published on 2 March 1994;

E3: B. Thurner et al., Journal of Immunological Methods, 1999, Vol. 223, pages 1 to 15;

E4: R.P. Lauener et al., Eur. J. Immunol., 1990, Vol. 20, pages 2375-2381;

E5: http://www.merckbiosciences.co.uk/htlm/cbc/proteinA_proteinG_§text2.htm, printed on 21 May 2007;

E6: http://www.merckbiosciences.co.uk/product/507861, printed on 21 May 2007;

E7: B. Passlick et al., Blood, 15 November 1989, Vol. 74, No. 7, pages 2527-2534;

E8: Pressestelle LMU, münchner ärztliche anzeigen, 8 November 2008, "Vorsicht bei Versuchen mit

Hitzeschockproteinen: Verunreinigungen können Immunreaktionen auslösen";

E9: P.K. Srivastava et al., Immunogenetics, 1994, Vol. 39, pages 93 to 98;

E10: M. Schnurr et al., Deutsches Ärzteblatt, 13 September 2002, Jg. 99, Heft 37; pages A2408 to A2416;

E11: Letter of Prof. Dr. Toni Lindl to the European Patent Office dated 18 October 2002;

E12: Letter of Prof. Dr. med. J. Hinrich Peters, undated;

E12a: H. M. Najar et al. European Journal of Cell Biology, 1990, Vol. 57, pages 339 to 346;

E13: Fax letter of Prof. DDr. J.C. Huber to the European Patent Office dated 23 December 2003 (6 pages);

E14: N. Romani et al., J. Exp.Med, July 1994, Volume 180, pages 83 to 93.

XIV. The submissions made by the appellant may be summarized as follows:

Fresh grounds for opposition put forward in appeal proceedings

The subject of the patent was not an invention but a scientific theory (Articles 100(a) and

52(2)(a) EPC 1973). The theory had been disguised and inadmissibly extended in examination proceedings. Evidence that the theory was wrong was provided by either document E3, which was an article published by one of the inventors after the filing date of the patent, or any of documents E11, E8, E9 and E10. The alleged invention was not susceptible of industrial application (Articles 100(a) and 57 EPC 1973).

Moreover, the claimed subject-matter lacked novelty (Articles 100(a) and 54 EPC 1973). It also extended beyond the content of the application as filed (Article 100(c) EPC 1973) because neither Pansorbin® nor *Staphylococcus aureus* were disclosed in the original application.

Admission of documents E11, E12 and E13 as evidence in appeal proceedings

Documents E11, E12 and E13 were filed as observations under Article 115 EPC 1973 during the examination proceedings. They were thus evidence forming part of the file and had to be considered by the board of its own motion.

Article 114(1) EPC 1973

The basic principle of *ex-officio* examination enshrined in Article 114(1) EPC 1973 was not restricted to the examination procedure but applied also to the procedure before the Boards of Appeal. Consequently, the board should not limit itself to the examination of the grounds for opposition and evidence submitted with the statement under Rule 55(c) EPC 1973, but must consider

all grounds for opposition, arguments and documents presented during the entire procedure, including those submitted during the examination procedure.

Article 100(b) EPC 1973

Since claim 15 did not specify the disease condition to be treated with the pharmaceutical composition prepared using a dendritic cell maturation factor, the patent did not disclose the purported invention in a manner sufficiently complete for it to be carried out by a person skilled in the art.

In order to carry out the alleged invention, pluripotent progenitor cells had to be obtained by leukapheresis, a method for which the appellant held a patent (document E2). Even though this was confirmed by a scientific article authored by one of the inventors of the patent in suit (document E3), in the patent itself the use of leukapheresis was not even disclosed, let alone was any information in this respect provided.

Article 100(a) in conjunction with Article 56 EPC 1973

Claims 1 to 6

Document E1 in combination with document E4

The opposition division correctly found that document E1, which described a method of producing mature dendritic cells using GM-CSF and IL-4 for inducing maturation, represented the closest state of the art. However, when finding that the method described in document E1 differed from the claimed

method in that a different starting material was used, the opposition division failed to take into account the actual content of E1 as well as further documents which represented the state of the art at the priority date claimed in the patent in suit.

As apparent from Figure 2 and the corresponding passage of the description on page 3S, document E1 described an *in vitro* method of preparing mature dendritic cells from progenitor cells which comprised two steps ("two broad stages" in the legend of Figure 2). In a first step ("proliferation phase"), precursor cells contacted with a differentiation composition comprising at least one cytokine (GM-CSF) developed to a "proliferate aggregate". In a second step ("maturation phase"), the aggregate developed to mature dendritic cells, which were exemplified by Langerhans cells. These cells were said to be useful for pharmaceutical purposes (cf. document E1, Summary, paragraph under the heading "Skin transplants" on page 4S).

In principle, the method according to claim 1 could be derived from E1 because this document already taught a skilled person working in the field of oncology the essential steps of a method of producing dendritic cells, which were essentially the same steps described in the patent in suit. A person skilled in the art would, without an undue burden of experimentation or the application of inventive skills, choose the antigens and differentiation compositions required in each particular case among those known in the art.

At the priority date, it was known that a CD14 positive cell population could be obtained by contacting a CD14

negative cell population with IL-4. This was readily apparent from the title and the summary on page 2378 of document E4, and also illustrated by the data provided in Table 1 on page 2378, in particular the column "%CD14+ cells" and the explanatory statements in chapter 3.3 ("Effects of CD14 expression of cytokines other than IL 4").

The use of a combination of GM-CSF and IL-4 for producing dendritic cells was known in the art. Moreover, contacting a CD14 positive, CD83 negative cell population with these cytokines inevitably resulted in the production of a cell population which was CD14 negative and CD83 positive. Thus, by contacting precursor cells with GM-CSF and IL-4 to induce their maturation as known in the state of the art, a person skilled in the art would inevitably perform step (a) of the method of claim 1.

The use of conditioned medium for inducing maturation of a cell aggregate obtained by proliferation of progenitor cells in order to obtain dendritic cells with the characteristic features of these cells was described in document E1 (cf. page 3S, left column, first paragraph under the heading "Maturation"). It was also apparent from E1 that the maturation process required some time to be completed. Thus, the essential features of step (b) of the method of claim 1 were anticipated by E1.

In addition, methods of inducing maturation of dendritic cells were known from document E7 published in 1989. This document described the production of dendritic cells from monocytes treated with cytokines.

Monocytes produced cytokines such as IL-1 and TNF. It was apparent from the passage starting from page 2533, left column, line 22 of document E7 that dendritic cells were obtained by adherence, like in the method of claim 1.

The use of Pansorbin® to isolate and stimulate lymphoid cells or adsorb immunoglobulins was well known in the art at the priority date, as shown in document E2 or evidenced by documents E5 and E6 and the references cited therein. Thus, it was obvious to use Pansorbin® to stimulate dendritic cells or monocytes.

For these reasons, the subject-matter of claim 1 should not be considered to involve an inventive step. The further features of the method specified in claims 2 to 6 were well known in the art, as it was apparent from documents E1 and E4 and the publications cited in the patent in suit.

Document E2

This document described a method for the isolation of cell fraction enriched with transformed cells circulating in the bloodstream of an individual, the cell fraction containing also leucocytes and/or lymphocytes. As apparent from page 4, lines 40 to 54, and section 3.2 on page 8 of document E2, the isolated cell fraction was then contacted with at least one cytokine, eg. IL-4 with the aim of stimulating antibody-producing cells.

Document E14

It was known from document E14 that dendritic cells could originate from $CD34^+$ progenitors present in cord blood and bone marrow, and that proliferation and maturation of dendritic cells were enhanced by the cytokine GM-CSF. Moreover, this document described that dendritic cells could also be obtained from adult blood from human healthy donors and that, when IL-4 was used to suppress monocyte development, the addition of GM-CSF led first to the formation of large proliferating dendritic cell aggregates and then, within 5-7 days, many nonproliferating progeny with the characteristic morphology and surface composition of dendritic cells.

Claims 7 to 10

The passage on page 2S, left column, first paragraph of document E1 was pertinent to the assessment of inventive step in respect of claim 7. The features included in claim 7, which were the same as in claim 1, had been shown to be derivable from the cited prior art documents. The further features specified in claims 8 to 10 represented obvious measures which a skilled person in the field of oncology would have taken without applying inventive skills. No evidence was required in this respect.

Claim 11

Steps (a) and (b) of the claimed assay to detect a dendritic cell maturation factor were derivable from the prior art documents cited in connection with

claim 1, and the further steps specified in claim 11 represented only simple measures which were within the skills of an average skilled person.

Claims 12 to 14

A culture medium as claimed was obtainable by the method described in document E1. The further features specified in claims 12 to 14 were obvious measures without any inventive merit.

Claims 15 to 18

These claims specified only simple measures within the knowledge of a skilled person in the field of oncology. As apparent from document E1, in particular the passage under the heading "Skin transplants" on page 4S, the use of dendritic cells for pharmaceutical purposes was well-known in the art.

XV. The submissions made by the respondents may be summarized as follows:

Fresh grounds for opposition put forward in appeal proceedings

The objection of lack of novelty represented a new ground for opposition which was not within the framework of the appeal and, therefore, should not be considered by the board. The same applied to the further objections raised shortly before the oral proceedings. Consent to their introduction was denied.

Admission of documents E11, E12 and E13 as evidence in appeal proceedings

The appellant had not relied on documents E11, E12 and E13 either in opposition proceedings or its statement of grounds of appeal. Being filed at such a late stage of the proceedings, these documents should not be admitted.

Article 100(a) in conjunction with Article 56 EPC 1973

Claims 1 to 6

Document E1 in combination with document E4

Starting from document E1 as the closest prior art, the technical problem to be solved was the provision of dendritic cells for pharmaceutical purposes. The method of E1 differed from that of claim 1 in that: a) the starting cell population was not specified in E1, and b) the two-step procedure used different compositions. In the method of E1, unspecific starting cells of the dendritic cell system were used, while the method in the patent required the expansion of dendritic cells from specific progenitor cells which E1 did not mention. Figure 2 of E1 taught the use of unspecified cytokines to induce maturation, rather than PBMC-conditioned medium or Pansorbin® as in the method of claim 1. Further, it was not clear from Figure 2 whether it referred to the *in vivo* or *in vitro* situation, or whether *in vivo* and *in vitro* conditions could be combined.

Document E4 was even less relevant to the granted claim 1 and did not give any hint towards the invention. To arrive at the conditions specified in claim 1, the skilled person had to select a starting population not disclosed in E1 and change two compositions without any suggestion or incentive. This could not be done without applying inventive skills.

Document E2

None of the features of the method of claim 1 could be derived from E2. This document described neither the starting population nor the use of the particular combination of cytokines specified in claim 1, let alone the use of PBMC conditioned medium for inducing maturation and render the mature cells stable.

Document E14

The authors of E14 did not appreciate that the dendritic cells prepared by the method described in this document were not stable. Consequently, they did not suggest any additional measures to be taken in order to obtain stable dendritic cells . A person skilled in the art had no motivation to try to modify the method described in E14.

XVI. The appellant requested that the decision under appeal be set aside and the patent be revoked.

XVII. The respondents requested that the appeal be dismissed.

Reasons for the Decision

Legal and factual framework of an appeal - Article 114 EPC 1973

1. According to Article 114(1) EPC 1973, in proceedings before it, the European Patent Office shall examine the facts of its own motion. In ***ex officio*** examination, the Office is not restricted to the facts, evidence and arguments provided by the parties and the relief sought.

2. The principle of ***ex officio*** examination and the extent to which it has to be applied in different proceedings before the European Patent Office have been the subject of several rulings of the Enlarged Board of Appeal, the instance responsible for deciding points of law referred to it by the Boards of Appeal and giving opinions on points of law referred to it by the President of the European Patent Office under the conditions laid down in Article 112 EPC 1973 (see Article 24(1) EPC 1973).

3. In decision G 9/91 (EPO OJ 1993, 408, point 2 of the Reasons), the Enlarged Board of Appeal judged that, whilst the principle of ***ex officio*** examination applies without restrictions in the proceedings before the Examining Division, in post-grant opposition proceedings its application must be restricted in order for the parties to be given equally fair treatment. As concerns appeal proceedings in opposition, which were considered to have the legal character of a contentious judicial procedure, the Enlarged Board of Appeal established that the principle of ***ex officio*** examination must be applied in an even more restricted

manner, both in the particular interest of legal certainty for the patent proprietor and the general interest of procedural expediency (G 1/99, OJ EPO 2001, 381, point 6.6 of the Reasons; G 9/91, ***supra***, point 18 of the Reasons).

4. The Enlarged Board of Appeal ruled that Article 114(1) EPC 1973 was no legal basis for an obligatory review of all grounds for opposition under Article 100 EPC 1973, including those not covered by the statement pursuant to Rule 55(c) EPC 1973 (see G 9/91, ***supra***, point 14 of the Reasons). Thus, an Opposition Division or a Board of Appeal is not obliged to consider grounds for opposition referred to in Article 100 EPC 1973 which go beyond the grounds properly submitted and substantiated in accordance with Article 99(1) in conjunction with Rule 55(c) EPC 1973.

5. While the opposition division may - exceptionally - consider other grounds for opposition which, ***prima facie***, would seem to prejudice the maintenance of the patent, in appeal proceedings fresh grounds for opposition may be considered only with the approval of the patent proprietor (see G 10/91, OJ EPO 1993, 420, Headnote, paragraph III). If a fresh ground for opposition is raised by an opponent on appeal, the board should only admit it into the proceedings if it considers the ground already ***prima facie*** highly relevant **and** the patent proprietor agrees to its introduction. If the patent proprietor opposes to the introduction of the fresh ground for opposition, the ground may not be dealt with in substance in the decision of the board of appeal at all (G 9/91, ***supra***, point 18).

Fresh grounds for opposition put forward by the appellant in appeal proceedings

6. By a letter filed one month before the oral proceedings, the appellant submitted fresh grounds for opposition which go beyond those covered by the statement under Article 99(1) in conjunction with Rule 55(c) EPC 1973 (see section III above), in particular grounds for opposition under Article 100(c), and Article 100(a) in conjunction with Articles 52(2)(a) and 57 EPC 1973 (see section XIII above).

7. Since in the present case the respondents (patent proprietors) denied approval (see paragraph XII above), the board is – in accordance with opinion G 10/91 (***supra***) - not empowered to admit and examine the fresh grounds for opposition put forward for the first time on appeal. Incidentally, the board notes that, having regard to the arguments and evidence submitted by the appellant in support of its new objections, none of the fresh grounds for opposition submitted by the appellant for the first time on appeal appears, ***prima facie***, to prejudice the maintenance of the patent in the granted form.

Admission and consideration of documents E11, E12 and E13

8. By virtue of Article 114(2) EPC 1973, an Opposition Division or a Board of Appeal is empowered to disregard facts or evidence which are not submitted in due time by the parties concerned.

9. The principle enshrined in Article 114(2) EPC 1973 has been applied in numerous rulings of the Boards of Appeal (for an overview see chapter VI.F of the Case Law of the Boards of Appeal of the European Patent Office, 5th edition 2006) and finds expression in the Rules of Procedure of the Boards of Appeal (RPBA), in particular in Articles 12 and 13 RPBA (OJ EPO 2007, 536).

10. Documents E11, E12 and E13 (see section XIII above) are copies of submissions made by third parties during the examination of the application on which the present patent was granted. The submissions were treated by the examining division as observations under Article 115 EPC 1973. As evidence in support of grounds for opposition under Article 100(a) and (b) EPC 1973, these documents were filed one month before the oral proceedings before the board. At the oral proceedings, the appellant maintained that the documents in question were part of the file and that, in its view, the board had no discretion whether or not to admit them as evidence into the proceedings, but was bound to consider them.

11. The board does not share this view. First, as far as documents E11, E12 and E13 have been submitted as evidence in support of fresh grounds for opposition raised for the first time on appeal, in particular lack of novelty, it is, in fact, correct that the board has no discretion when deciding whether the documents are considered or disregarded. Since according to decision G 10/91 (*supra*) the board cannot consider the fresh grounds of opposition put forward by the appellant for the first time in appeal proceedings - as the patent

proprietor opposed to their introduction into the proceedings -, it cannot consider evidence submitted in their support either.

12. Second, in the board's view, as far as documents E11, E12 and E13 have been submitted as evidence in support of grounds for opposition put forward in the statement under Rule 55(c) EPC 1973 (ie. grounds for opposition under Article 100(b) and Article 100(a) in conjunction with Article 56 EPC 1973), they were not filed in due time and, consequently, the board is empowered to exercise the discretion conferred by Article 114(2) EPC 1973 to disregard them.

13. The question whether or not evidence has been filed in due time has to be decided taking into account the circumstances of the particular case. In the present case, the grounds for opposition under Article 100(b) and Article 100(a) in conjunction with Article 56 EPC 1973 were put forward within the opposition period provided for in Article 99(1) EPC 1973. Thus, in principle, any evidence in support of these grounds had to be submitted within the opposition period, unless there were valid reasons not to do so.

14. In the statement under Rule 55(c) EPC 1973, only the observations under Article 115 EPC 1973 filed as document E13 in appeal proceedings were mentioned as evidence in support of the ground for opposition under Article 100(b) EPC 1973, in particular in connection with the objection that the patent failed to disclose leukapheresis as the technique which must be applied in order to prepare the pluripotent cells required as starting material in the method according to claim 1.

Neither a copy of document E13 nor of documents E11 and E12 was filed within the opposition period or at a later stage of the opposition proceedings.

15. The evidence in question could possibly have been submitted together with the statement of grounds of appeal, as a reaction to the adverse decision of the opposition division. However, in its statement of grounds the appellant neither relied on documents E11, E12 and E13 nor filed copies thereof. Incidentally, it should be also noted that the adverse finding of the opposition division concerning the objection of lack of disclosure of leukapheresis in the patent was not even contested by the appellant in its statement of grounds of appeal.

16. It was only in its submission in reply to the communication under Article 15(1) RPBA sent by the board in preparation for the oral proceedings that the appellant relied on documents E11, E12 and E13 and filed copies thereof. However, no reasons were given which justified the documents having been submitted at this late stage of the proceedings, except for the remark that the documents in question were already "on file". It should be noted here that the evidence in question was certainly not filed pursuant to directions of the board (see Article 12(1)(c) RPBA), as the board had given no directions in this respect in its communication.

17. In view of the circumstances outlined above, the board judges that the evidence in documents E11, E12 and E13 on which the appellant relied for the first time in its submission filed one month before the oral proceedings

before the board, was not submitted in due time. The fact that these documents were identical to observations filed by third parties during the examination proceedings, a copy of which was - as the appellant stressed - "on file", does not change this judgement because, in the board's view, the decisive issue is whether or not the appellant relied on these documents in due time for the board to be able to evaluate any possible evidence contained therein, and for the respondents to react thereto.

18. In this respect, it is worth to note that in document E11, which is entitled "Gutachten und Einspruch zum Patent ..." and begins with the introductory remark "***Dieses Patent ist eine völlig kritiklose und wissenschaftlich wirre Zusammenstellung aller möglichen und auch keineswegs neuen Zellkulturtechniken, um alles nur Erdenkliche auf diesem Gebiet abzudecken, ohne irgendwelche konkreten Methoden und Ergebnisse nachvollziehbar darzustellen bzw. zu definieren***", deals with claims 15 to 17 as on file at the time the observations were drafted - which appear to correspond to claims 12 to 14 as granted - and not less than 16 scientific articles are cited in support of the author's view. However, except for one of these citations, which is referred to in this decision as document E12a, copies of the publications cited in E11 were never submitted for consideration by the examining division, the opposition division or the present board.

19. As concerns document E12, which contains little more than a short introduction and a list of scientific articles in the field of dendritic cells published by

the author of the observations and his group, only one of the cited publications - again document E12a – has been filed.

20. Finally, in the observations filed by the appellant as document E13, which deal briefly with the issues of lack of sufficient disclosure, in particular with regard to leukapheresis, and inventive step, 39 scientific articles are cited. Even though the content of some of the cited articles is briefly summarised in the observations, copies of the publications were never filed.

21. ***Prima facie***, the observations filed as documents E11, E12 and E13 do not appear to raise any further issues in connection with the grounds for opposition of lack of sufficient disclosure and lack of inventive step which have not been raised by the appellant in its submissions in opposition proceedings and decided upon by the opposition division in the decision under appeal. As concerns the numerous scientific articles cited in these documents, the board observes that, if the appellant wished to have them considered as evidence, it would have been its duty to provide copies in due time, in order for the board to be able to study them and the other party to submit arguments and counter-evidence.

22. For these reasons, the board, exercising its discretion under Article 114(2) EPC 1973, decides to disregard documents E11, E12 and E13.

Admission of document E14 into the appeal proceedings

23. Document E14, which was filed during the oral proceedings before the board, is identical to a document cited and discussed during the examination of the patent application on which the present patent was granted.

24. Since in its communication under Article 15(1) RPBA, the board indicated that this document could become subject of discussion at the oral proceedings, and the respondents had sufficient time to study the document and prepare their observations in this respect, both the board and the respondents are familiar with the content of document E14. As the respondents agreed to its introduction in the appeal proceedings, the board decided to admit and consider it.

Article 100(b) EPC 1973

Claim 15

25. In the decision under appeal, the invention claimed in independent claims 1, 11 and 15 as granted was found to be disclosed in the description of the patent specification in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. In particular, the opposition division overruled the opponent's objection that the method used in Example 1 did not allow the isolation of a sufficient amount of starting material for a clinical use, on the grounds that Article 83 EPC 1973 could not be construed to require the disclosure of an industrially or clinically feasible manner to carry out

the invention. The opposition division considered further that, since the patent described different procedures for obtaining the starting material of the method of claim 1, sufficient guidance was provided to the skilled person in respect of the starting material. Moreover, paragraphs [0057] and [0058] of the patent were found to provide sufficient guidance in respect of the differentiation and the maturation media required in order to perform the method of claim 1, and the fact that a PBMC conditioned media was not a fully defined media was found not to be prejudicial with regard to Article 100(b) EPC 1973.

26. None of these findings was contested by the appellant in its statement of grounds of appeal. The sole finding of the opposition division in respect of Article 100(b) EPC 1973 questioned by the appellant in the statement of grounds concerned claim 15, which is drafted as a "second medical use" claim in the "Swiss-type" form (see section II above). The appellant maintained the objection raised in opposition proceedings that, since the particular disease condition to be treated was not specified in claim 15, the ground of opposition of Article 100(b) EPC 1973 prejudiced the maintenance of the patent as granted.

27. While it is true that in claim 15 the disease condition to be treated or prevented is defined only in functional terms, and that a particular disease, illness or ailment is not specified, in the board's view the appellant's objection under Article 100(b) EPC 1973 is not justified. It has not been disputed by the appellant that, with the information provided in the patent supplemented by the common general knowledge

in the pertinent technical field at the priority date, a person skilled in the art was able to prepare a pharmaceutical composition using PBMC conditioned medium. Nor has been disputed that claim 15 relates to a therapeutic application of the pharmaceutical composition containing PBMC conditioned medium.

28. The patent in suit discloses not only that the methods and compositions provided by the invention are useful for activating an individual's T cells against specific antigens, but also that "[T]he ***activation of an individual's T cell is useful for the prevention or treatment of disease, for example killer cells to treat or vaccinate against cancer or infection***" (see paragraph [0017] of the patent). Thus, the patent as a whole discloses specific examples of disease conditions ("***cancer or infection***") falling under the functional definition provided in claim 15, which, according to the claimed invention, are prevented or treated using a pharmaceutical preparation comprising PBMC conditioned medium.

29. In the board's view, it appears from the arguments put forward by the appellant that its objection does not concern the - allegedly insufficient - disclosure in the patent as granted, but rather the extent of the protection provided by claim 15. Hence, the objection raised by the appellant under Article 100(b) EPC 1973 seems to be, actually, an objection concerning the clarity and breath of the claim.

30. Since neither lack of clarity nor broad claims are grounds for opposition under Article 100 EPC 1973 which can be validly put forward against the claims of a

patent as granted, the appellant's objection to claim 15 must fail.

Further objections under Article 100(b) EPC 1973 in respect of other claims

31. In its reply to the communication of the board under Article 15(1) RPBA filed one month before the oral proceedings, the appellant raised objections to the further claims relying on fresh documents E8, E9 and E10 filed together with the reply, and document E3 filed at the outset of the opposition proceedings (see section XIII above). Additionally, at the oral proceedings documents E2 and E11 were cited as further evidence not only for the ground for opposition of Article 100(b) EPC 1973, but also for the fresh ground under Article 100(a) in connection with Article 57 EPC 1973, both grounds for opposition being, in the appellant's view, closely related.

32. In response to the board's question why the further objections under Article 100(b) EPC 1973 had not been raised in the statement of grounds of appeal, the appellant indicated that document E8 could not have been filed with the statement of grounds of appeal because it was published in 2008, ie. after expiry of the time period specified in Article 108 EPC 1973. Even though it admitted that documents E2 and E3 had been on file from the outset of the opposition proceedings, in its view the objections relying on these documents were not belated and, therefore, had to be considered by the board.

33. This argument cannot be accepted. According to Article 12(2) RPBA, the statement of grounds of appeal must contain the complete case of a party appealing an adverse decision. In the present case, there is no apparent reason why the further objections were raised by the appellant only one month before the date of the oral proceedings before the board, especially in view of the fact that the claims as granted have been the sole request of the respondents throughout the opposition and appeal proceedings. In the board's view, both the objections and the documents filed as evidence in their support (except for E8) have not been submitted in due time because they could have been submitted already in opposition proceedings or, at the latest, together with the statement of grounds of appeal. Moreover, p*rima facie*, they do not appear to prejudice the maintenance of the patent as granted. For these reasons, both the further objections and evidence are disregarded.

Article 100(a) in conjunction with Article 56 EPC 1973

Claim 1

Document E1 as the closest prior art in combination with document E4

34. In the decision under appeal, document E1 was considered to represent the closest prior art. The opposition division found that the method of obtaining mature dendritic cells described in this document differed from the method of claim 1 in (a) the starting cell population and (b) the compositions used in each

of the two steps of the method (ie. differentiation and maturation).

35. While both parties agreed in that document E1 represents the closest prior art, the findings of the opposition division on the features distinguishing the method of claim 1 from those described in E1 were contested by the appellant.

The starting cell population

36. The relevant passage of document E1 is considered to be the passage bridging pages 2S and 3S, where it is stated that:

"In liquid culture systems, mouse and human dendritic cells can expand from proliferating progenitors in blood, liver, and bone marrow. [...] In the human system, progenitors lie within the CD34$^+$ subset of cord blood and marrow ..."

37. As the opposition division found in its decision, the board observes that the passage of document E1 quoted above does not expressly mention a population of CD14 positive and substantially CD83 negative pluripotent cells as the cell population from which stable mature CD83 positive dendritic cells can be obtained.

38. In support of its line of argument on this issue, the appellant cited documents E4, E7 and E12a (see section XIII above).

39. In the appellant's view, document E4 showed that, when CD14 negative cells are treated with IL-4, a CD14

positive cell population is obtained. This document describes that recombinant IL-4 down-regulates the expression of CD14 on normal human monocytes (see title and the first sentence of the abstract), and the data provided in Table 1, which are commented and analysed in chapter 3.3, show that IL-4 caused a significant decrease of the expression of CD14 in normal human monocytes isolated from peripheral blood, the percentage of CD14 positive cells in the cell population falling from 73% + 3 prior to the incubation with IL-4, to 36% + 6 after the incubation, whereas no significant decrease was observed when the cells were incubated with other cytokines, ***inter alia***, GM-CSF. Whilst IL-4 is described in document E1 as a useful cytokine for the generation of dendritic cells in culture, the board is not able to find in this document any indication that a population of CD14 positive and substantially CD83 negative pluripotent cells can be used as progenitor cells from which mature stable dendritic cells develop.

40. Document E7 was cited by the appellant in its statement of grounds of appeal as evidence for a CD14 positive monocyte subpopulation identified and characterised in human peripheral blood. It is stated in document E7 that the $CD14^+/CD16^+$ monocyte subpopulation described therein might represent immature precursor cells (see page 2533, right column, line 12). However, document E7 neither discloses nor suggests that the cells of the identified monocyte subpopulation are CD14 positive and substantially CD83 negative pluripotent cells and may serve as precursors for mature dendritic cells; on the contrary, a relationship between the $CD14^+/CD16^+$ monocyte subpopulation and peripheral blood dendritic

cells is said to be unlikely (see page 2533, left column, second paragraph, lines 7 to 10).

41. The appellant relied on the subsequent passage of E7 which starts on page 2544, second paragraph, line 10 and reads:

"Since dendritic cells are usually isolated by an overnight adherence procedure a direct comparison, however, is difficult. Analysis of light scatter properties indicates that the $CD14^{+}/CD16^{+}$ cells are similar to the $CD14^{++}$ monocytes. Both granularity and cell size were somewhat lower but clearly distinct from lymphocytes."

42. The board is unable to see in this passage any indication that the described $CD14^{+}/CD16^{+}$ monocyte subpopulation may be a population of CD14 positive and substantially CD83 negative pluripotent cells as required in claim 1, let alone the teaching that mature dendritic cells can be obtained starting from the identified monocyte subpopulation.

43. Document E12a, to which the appellant referred in connection with the "starting material" issue, describes that human peripheral blood monocytes can differentiate ***in vitro*** into accessory cells reminiscent of lymphoid dendritic cells when cultivated in serum-free medium.

44. However, whether or not the monocyte preparation from buffy coats of healthy blood donors described in document E12a is "***a population of CD14 positive and substantially CD83 negative pluripotential cells***"

capable of developing to mature dendritic cells, as specified in claim 1, cannot be ascertained, and the appellant has not provided any evidence in this respect. It should be noted that, since the preparation of monocytes described in document E12a is not depleted of T and B cells, it is likely to include cells other than CD14 positive and substantially CD83 negative pluripotent cells, and may therefore be unsuitable for producing stable mature dendritic cells. Moreover, it appears that the statement of the authors of document E12a that "*[I]t remains an unsolved question whether DC* [dendritic cells, note by the board] *are derived from monocytes or represent a separate lineage.*" (see page 344, right column, first paragraph under the heading "Discussion") would discourage rather than provide a motivation for the skilled person to use of the monocyte preparation described in this document as starting material for producing stable mature dendritic cells.

45. In view of the findings above, the board concludes that, contrary to the appellant's view, none of documents E4, E7 or E12a contain any hint towards the use of CD14 positive and substantially CD83 negative pluripotent cells as starting material for obtaining stable mature dendritic cells.

Proliferation and maturation steps

46. In the decision under appeal, the opposition division observed that a multitude of compositions suitable for the maturation of dendritic cells were discussed in document E1, and cited as examples media containing GM-CSF, TNF-alpha or further cytokines (see page 7, second

full paragraph of the decision under appeal). This has not been disputed by either party.

47. In fact, document E1 describes that the proliferative phase can be induced using different cytokines or combinations of cytokines, in particular GM-CSF alone, GM-CSF in combination with TNF-α and GM-CSF in combination with IL-4 (see chapter "Development from Proliferating Progenitors" bridging pages 2S and 3S). It is also stated in E1 that "[*T]o date, GM-CSF must be added to all culture systems that generate dendritic cells.*" (see page 3S, left column, lines 8 to 10) and that "*... IL-4 is useful in unfractionated adult human blood*".

48. As concerns compositions that trigger the maturation phase, document E1 mentions the use of conditioned medium for the maturation of dendritic cells from human blood (see page 3S, left column, second paragraph with the heading "Maturation", last two sentences) and of two specific cytokines, GM-CSF and TNF-α, for cells cultured from other sites, e.g. spleen, lung, heart, and kidney (see page 3S, right column, first full paragraph).

The technical problem to be solved

49. The opposition division formulated the objective technical problem to be solved starting from document E1 as the closest prior art, as the provision of a method of producing mature dendritic cells suitable for pharmaceutical purposes.

50. It is disclosed in the patent that mature dendritic cells produced by the methods known at the priority date were not suitable for therapeutic purposes because they were not stable and reverted to a less stimulatory state when the cytokines used to induce proliferation and maturation were removed. The lack of stability of the mature dendritic cells is in fact supported by the comparative results shown in Table 1 (compare first and second row, ratio 900:1) and Figure 1 of the patent. Since no arguments or evidence to the contrary have been submitted by the appellant, the board accepts that the poor stability of the mature dendritic cells obtained by the methods according to the prior art may in fact pose a efficacy problem when they are used as adjuvants in immunotherapy. Thus, the technical problem formulated by the opposition division in its decision seems to be correct.

51. It was not disputed by the appellant that the mature dendritic cells obtained by the method according to claim 1 are more stable and, therefore, more suitable for pharmaceutical purposes that the mature dendritic cells of the prior art. Thus, the problem formulated by the opposition division is considered to be solved by the method of claim 1.

52. None of the documents cited by the appellant describe or suggest that the mature dendritic cells obtained by the methods described therein are not stable and may revert to a less stimulatory state when the cytokines used for inducing maturation are removed. Thus, at the relevant date a person skilled in art did not have a particular motivation to modify any of the different methods disclosed in document E1 for obtaining mature

dendritic cells. Moreover, even if the skilled person may have thought of improving the existing methods, there is no indication in the cited documents that stability in the absence of cytokines could be improved, let alone how to achieve this improvement.

53. The appellant argued that, at the relevant date, conditioned media were known to contain small amounts of growth factors and were widely used to support the growth of cells in vitro. While this may be true, the board observes that the technical contribution of the invention is not restricted to the use of conditioned medium for growing dendritic cells. Rather, the method according to the invention combines the selection of a particular cell population of pluripotent cells as starting material, the use of a specific combination of cytokines for inducing proliferation of the precursor cells, and the use of PBMC conditioned medium or Pansorbin® for inducing maturation to stable mature dendritic cells.

54. This combination is not obvious in view of document E1, either alone or in combination with E4. Figure 2 in document E1, to which the appellant referred, shows graphically that, in their development dendritic cells require a proliferative phase and a maturation phase. However, the nature of the progenitor cells is not specified and GM-CSF or GM-CSF + TNF-α are used for the induction of the proliferation phase. Also, although it is indicated that the development of immature dendritic cells require (unspecified) cytokines, there is no indication whatsoever that such cytokines may be contained in PBMC conditioned medium or induced by Pansorbin®.

55. With respect to the - allegedly obvious - use of the latter compound for inducing maturation of dendritic cells, the appellant referred to documents E5 and E6. Apart from the fact that the publication date of these internet print-outs cannot be established without doubt, the board notes that neither these documents nor any of the scientific articles cited therein, a copy of which was submitted by the appellant, suggests using Pansorbin® in whatever manner for obtaining mature dendritic cells.

56. For the reasons given above, the appellant's line of argument on lack of inventive step relying on documents E1 and E4 fail to convince the board.

Document E2

57. At the oral proceedings, the appellant relied on document E2 as closest prior art. However, this document, which relates to the stimulation of antibody-producing cells using a cell fraction isolated from human blood, does not mention dendritic cells at all. Moreover, even if it were accepted that – as the appellant maintained - a cell fraction isolated following the instructions given in E2 would contain pluripotent cells as used as starting material in the method according to claim 1, there is no indication in this document - apart from the incidental use of IL-4 – that may suggest to a skilled the person a method of inducing the maturation of the dendritic cell precursors and obtaining stable mature dendritic cells suitable for pharmaceutical purposes, as claimed in the patent. Thus, the attack based on document E2 must fail.

Document E14

58. The content of document E14 was discussed extensively during the examination of the application on which the present patent was granted, but it was at the oral proceedings before the board that the appellant raised for the first time an objection of lack of inventive step relying on this document. The content of the document is also summarised in the patent (see paragraph [0007], in particular lines 49 to 51 on page 3 of the patent), and the drawbacks associated with the method of E14 are described (see lines 52 to 55).

59. The respondents admitted that, in the method described in document E14 precursor cells obtained from blood are contacted with GM-CSF and IL-4 as in step (a) of the method according to claim 1 as granted. In their view, however, the technical contribution of the invention was, first, recognising that the dendritic cells obtained in E14, although having the characteristic morphology and surface composition of mature dendritic cells, were not stable and reverted to a more inmature state when the cytokines were removed, and, second, finding out that contacting the cells with PBMC conditioned medium or Pansorbin® could prevent the reversion. As stated above in connection with document E1, the board finds the respondents' arguments persuasive, and considers that the appellant has not been able to refute them convincingly.

60. Consequently, starting from any of documents E1, E2 or E14 as the closest prior art, the subject-matter of

claim 1 is considered to involve an inventive step within the meaning of Article 56 EPC 1973. The same finding applies to the dependent claims 2 to 6.

Claims 7 to 10

61. The arguments put forward and the documents relied upon by the appellant in respect of claims 7 to 10, which are directed to methods of activating T cells using stable mature dendritic cells prepared by the method of claims 1 to 6, were essentially the same as for claim 1. For the same reasons given above in connection with this claim, the board is not persuaded that the subject-matter of claims 7 to 10 lacks an inventive step.

Claim 11

62. The appellant failed to indicate any specific passage of the documents cited in respect of claim 1 which can be considered pertinent to the issue of inventive concerning an assay to detect a dendritic cell maturation factor as claimed in claim 11. In fact, none of the cited documents suggest such an assay. The objection to claim 11, thus, fails.

Claims 12 to 14

63. Also the objection of lack of inventive step raised against claims 12 to 14 relying on document E1 should fail, because the appellant has not provided any evidence in support of its argument that a culture medium as claimed is obtainable by a method described in document E1. It should be noted that document E1

discloses several methods of obtaining dendritic cells, but none of them uses a medium containing GM-CSF, IL-4 **and** PBMC conditioned medium. Incidentally, the objection raised by the appellant appears to be an objection of lack of novelty which, in principle, cannot be dealt with in substance as the respondents did not give their consent to the introduction of fresh grounds for opposition.

Claims 15 to 18

64. The opposition division found that, while document E1 described the use of conditioned media for inducing the maturation of dendritic cells ***in vitro***, it did not suggest any pharmaceutical use whatsoever. Consequently, the subject-matter of claim 15 was considered to involve an inventive step.

65. The appellant has not put forward any arguments or evidence in support of its assertion that a pharmaceutical use of PBMC conditioned media was an obvious measure. The sole passage cited by the appellant in connection with a medical use (document E1, passage under the heading "Skin transplants" on page 4S) concerns the behaviour of **dendritic cells** in skin transplants, but not the use of PBMC conditioned media for the preparation of a pharmaceutical composition, as claimed in claim 15.

66. Thus, the board regards the appellant's objection as being unjustified.

Conclusion

67. The arguments and evidence presented by the appellant and considered above do not persuade the board that the decision under appeal must be set aside.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani