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Datasheet for the decision of 23 February 2010

Case Number: T 1423/08 - 3.3.08

Application Number: 98901221.6

Publication Number: 0986635

IPC: C12N 5/00

Language of the proceedings: EN

Title of invention:
Embryonic stem cell serum replacement

Applicant:
Life Technologies Corporation

Opponent:
-

Headword:
Medium supplement/LIFE TECHNOLOGIES

Relevant legal provisions:
EPC Art. 84, 54

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request and auxiliary requests I to IV - clarity (no)"

Decisions cited:
-

Catchword:
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Case Number: T 1423/08 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 23 February 2010

Appellant: Life Technologies Corporation
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 19 February 2008 refusing European application No. 98901221.6 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent application no. 98 901 221.6, published as International application WO 98/30679 (referred to in this decision as "*the application as filed*"), was refused by the examining division on the grounds that the claim request filed on 21 August 2007 did not fulfil the requirements of Articles 84, 83 and 56 EPC.

II. The request before the examining division contained 59 claims, wherein claims 1 and 19 read as follows:

"1. Serum-free, eukaryotic cell culture medium supplement comprising one or more lipid-rich albumins or albumin substitutes, one or more vitamins, one or more transferrins or transferrin substitutes, one or more insulins or insulin substitutes, one or more collagen precursors, and one or more trace elements, wherein a basal cell culture medium supplemented with said supplement is capable of preventing differentiation of embryonic stem cells."

"19. A serum-free eukaryotic cell culture medium comprising a basal cell culture medium supplemented with the serum-free cell culture supplement according to any one of claims 1 to 15, wherein said supplemented culture medium is capable of supporting growth of embryonic stem cells in a serum-free culture."

III. The examining division considered that the terms "lipid-rich albumins", "albumin substitutes", "transferrin substitutes" and "insulin substitutes" used in *inter alia* claim 1 lacked clarity (Article 84 EPC). A further objection for lack of clarity and

insufficiency of disclosure was raised with respect to the trade names AlbuMAX®I and AlbuMAX®II used in several dependent claims when defining albumin substitutes (Articles 83 and 84 EPC). The examining division considered that, in the absence of any evidence for a technical effect linked to the feature "lipid-rich albumin", the replacement of fatty acid-free albumin as used in document D18 (*infra*) for normal albumin (containing fatty acid, lipid-rich) or for AlbuMAX (containing a higher lipid content) was an arbitrary choice among the different commercially available albumins. Therefore, inventive step was denied for claim 1 (Article 56 EPC), and consequently for all remaining claims.

IV. On 17 April 2008, the applicant (appellant) filed a notice of appeal. The statement setting out the grounds of appeal was filed on 19 June 2008 together with a first, second, third and fourth auxiliary requests. On 8 July 2008, the appellant filed the main request, which had been accidentally omitted from the statement of grounds.

V. The examining division did not rectify its decision and the case was remitted to the board of appeal (Article 109(2) EPC).

VI. On 13 August 2008, the appellant requested the board to use its discretion to admit the main request into the appeal proceedings.

VII. On 8 October 2009, the board summoned the appellant to oral proceedings and sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards

of Appeal (RPBA) indicating its preliminary, non-binding opinion on substantive issues. In particular, the board indicated that the main request could be admitted into the proceedings and that none of the appellant's requests fulfilled the requirements of Articles 84 and 54 EPC.

VIII. On 8 February 2010, the appellant informed the board of its intention not to attend the oral proceedings. No submissions were made regarding substantive issues.

IX. Oral proceedings took place on 23 February 2010 in the absence of the appellant.

X. Claims 1 and 15 to 18 of the **main request** read as follows:

"1. Serum-free, eukaryotic cell culture medium supplement comprising one or more albumins, one or more vitamins, one or more transferrins or transferrin substitutes, one or more insulins or insulin substitutes, one or more collagen precursors, one or more trace elements, and one or more antioxidants wherein a basal cell culture medium supplemented with said supplement is capable of preventing differentiation of embryonic stem cells."

"15. A serum-free eukaryotic cell culture medium comprising a basal cell culture medium supplemented with the serum-free cell culture supplement according to any one of claims 1 to 14,
wherein said supplemented culture medium is capable of supporting the growth of embryonic stem cells in a serum-free culture."

"16. The serum-free, eukaryotic cell culture medium according to claim 15 wherein said medium is a 1X medium formulation."

"17. The serum-free, eukaryotic cell culture medium according to claim 16 wherein said medium is more concentrated than a 1X medium formulation."

"18. The serum-free, eukaryotic culture medium according to claim 17 wherein the final concentration of said supplement is about 0.5% to about 90%."

XI. The claims of the **first auxiliary request** were essentially identical to those of the main request, except for the introduction of the definition of the transferrin and insulin substitutes (claims 4 and 6 of the main request) into claim 1.

XII. Claims 1, 15 and 18 of the **second auxiliary request** read as follows:

"1. Use of a serum-free, eukaryotic cell culture medium supplement comprising one or more albumins, one or more vitamins, one or more transferrins or transferrin substitutes, one or more insulins or insulin substitutes, one or more collagen precursors, and one or more trace elements and one or more antioxidants as a supporter of embryonic stem cell growth which does not promote embryonic stem cell differentiation in a serum free culture medium which is capable of supporting the growth of embryonic stem cells in serum-free culture and comprises in admixture the supplement and a basal medium."

"15. Use of a serum-free eukaryotic cell culture medium as defined in any one of claims 1 to 14, in supporting the growth without differentiation of embryonic stem cells in a serum-free culture."

"18. Use of a serum-free, eukaryotic culture medium according to claim 15 wherein the final concentration of said supplement is about 0.5% to about 90%."

XIII. The claims of the **third auxiliary request** were essentially identical to those of the second auxiliary request, except for the introduction of the definition of the transferrin and insulin substitutes and of one or more amino acids (claims 4, 6 and 8 of the second auxiliary request) into claim 1. Moreover, claim 12 of the third auxiliary request read as claim 15 of the second auxiliary request with the additional presence of a basal cell culture medium.

XIV. The claims of the **fourth auxiliary request** read essentially as those of the third auxiliary request except for the fact that it contained only claims 1 to 19 thereof.

XV. The following document is mentioned in the present decision:

D18: T. Atsumi et al., Develop. Growth & Differ., 1993, Vol. 35(1), pages 81 to 87.

XVI. The appellant's arguments may be summarized as follows:

Admissibility of the main request

The scope of both the independent and dependent claims of the main request was directly and unambiguously derivable from the appellant's statement of the grounds of appeal, which described in detail the exact amendments made to each claim and where basis for each amendment could be found in the application as filed. Thus, the subsequent filing of the request, which had been accidentally omitted, did not introduce any new issues, but simply repeated in a different format the scope of the main request previously defined. The request was filed as soon as its absence was brought to the appellant's attention and well in advance of the case being remitted to the board. In an *ex parte* case, the late filing of the main request did not prejudice any third party.

Article 84 EPC
Main request and second auxiliary request

The terms "transferrin substitutes" and "insulin substitutes" in claim 1 were clear and well understood by the skilled person. According to the case law, essential technical features could be expressed in general functional terms, if such features could not otherwise be defined more precisely without restricting the scope of the invention and if the description provided instructions sufficiently clear for the skilled person to put the invention into practice with no more than a reasonable amount of experimentation. These criteria were satisfied. The role of transferrin

in vivo and in cell culture was well known in the art, namely to bind iron and to enable controlled availability of iron to the cells. Similarly, insulin was known to be used in cell culture media as a growth factor and it was also known that zinc compounds could be used in place of insulin. A range of substitutes existed for both insulin and transferrin as shown in the description of the application. In order to ensure a fair protection, these compounds had to be defined functionally. Listing specific compounds was an unfair limitation of the scope of protection as such a list could never be regarded as complete.

First, third and fourth auxiliary requests

The terms "transferrin substitutes" and "insulin substitutes" were clearly defined in these requests by the introduction of a specific list of compounds.

Article 54 EPC
Main and first auxiliary request

The claims required the presence of one or more antioxidants to be in the serum-free, eukaryotic culture medium supplement of the invention. Antioxidants did not form part of any of the media described in prior art document D18.

Second, third and fourth auxiliary requests

The disclosure of document D18 was limited to an analysis of activin on the growth of PCC3 cells. The study of embryonic stem cells (ESC) was limited to the analysis of their proliferation on a serum-free medium.

Document D18 was not concerned with ESC differentiation nor did it disclose the use of serum-free media to prevent ESC differentiation. There was only a reference to the ability of a serum-free conditioned medium of KCF fibroblastic cells (KCM) to induce differentiation of erythroid cells, this being a typical activity of activin. However, these cells were not ESC. Therefore, the document did not anticipate claims directed to the use of a serum-free eukaryotic culture supplement in preventing ESC differentiation.

XVII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of either the main request filed on 8 July 2008 or one of the auxiliary requests I to IV filed with the statement of grounds of appeal.

Reasons for the Decision

Admissibility of the main request into the appeal proceedings

1. Although referred to in the statement of grounds of appeal, the main request was filed only subsequently. Its contents were also discussed in detail in the appellant's statement of grounds of appeal when explaining the relevance of that request and the amendments introduced to overcome the objections raised by the examining division in the decision under appeal. It was thus immediately clear that the request had been unintentionally and accidentally omitted. Indeed, the omission was immediately noticed by the examining division. Once informed, the appellant provided the

main request without delay and before the case was remitted to the board.

2. In view of these circumstances, the board considers that the appellant's main request can be admitted into the appeal proceedings under Article 13(1) RPBA.

Article 84 EPC
Main request

3. There are a number of objections under Article 84 EPC to this request. These objections were outlined in the communication of the board sent with the summons to oral proceedings and they have remained unanswered by the appellant which has decided not to attend the oral proceedings (cf. points VII to IX *supra*). The objections are outlined hereinafter.

4. Claim 1 is directed to a product, namely a (serum-free, eukaryotic cell culture) medium supplement, which is characterized by its chemical composition defined **in general terms** by the presence of seven ingredients out of eight possible ingredients originally indicated in the application as filed ("*... combining one or more ingredients selected from the group ...*") (cf. *inter alia* page 3, lines 20 to 25 of the application as filed). These ingredients are also defined **in general terms**, such as "*one or more trace elements*", "*one or more antioxidants*", etc. (cf. *inter alia* list on page 12, line 27 to page 13, line 9). The claimed product is further defined by the result to be achieved, namely "*capable of preventing differentiation of embryonic stem cells*", in an indirect and ambiguous manner, since that result is achieved only by the

combination of the claimed medium supplement with "*a basal cell culture medium*" which is itself undefined. As a consequence thereof, the functional requirement defining the claimed product (medium supplement) actually depends on another product (basal cell culture medium) that is completely uncharacterized. The characterization of the claimed product in this manner does not fulfil the requirements of Article 84 EPC since the actual composition of that product is ambiguous and unclear.

5. As objected to in the decision under appeal, the terms "*transferrin substitutes*" and "*insulin substitutes*" are open to subjective interpretation. In the application as filed, these substitutes are defined only by reference to the results obtained when using the supplement of the invention ("*any compound which may replace transferrin in the supplement of the invention to give substantially similar results as tranferrin*" and "*any zinc containing compound which may be used in place of insulin in the supplement of the invention to give substantially similar results as insulin*", cf. page 9, lines 4 to 6 and lines 18 to 20), i.e. capable of preventing differentiation of embryonic stem cells (ESC) when supplemented to a basal cell culture. This definition does not characterize the substitutes in a clear and unambiguous manner as it does not provide a limitation to those compounds that have the same or similar function as that of transferrin (such as iron chelate) and/or that of insulin (such as cell growth stimulatory). It is much broader and ambiguous including any (undefined) compound which, although unrelated to transferrin and/or to insulin, might nevertheless achieve the same result (preventing ESC

differentiation) when used in a serum-free eukaryotic cell culture medium supplement. This is all the more so since the examples given in the application of known transferrin and insulin substitutes are not limiting ("*include but are not limited*") (cf. page 9, lines 6 to 9 and 20 to 21) and the referred to (desired) result (prevention of ESC differentiation) might be dependent on the specific basal cell culture medium admixed with the supplement. Thus, the board does not see any reason to deviate from the examining division's conclusions in this respect.

6. The following additional issues are also of relevance in the context of Article 84 EPC:

6.1 The ability to prevent ESC differentiation results from the combination of the claimed serum-free supplement with a basal cell culture medium (cf. point 4 *supra*). In the application as filed the basal cell culture medium is defined as being serum-free and being such that, upon combination with the disclosed serum-free supplement, it supports ESC growth and expansion without promoting or inducing ESC differentiation (cf. *inter alia* page 3, lines 12 to 19, page 14, line 22 to page 15, line 5). Apart from the latter feature, none of the other essential features is present in claim 1.

6.2 The wording of claim 15 is also ambiguous since it is not clear whether the ability to support ESC growth in a serum-free culture refers to the supplemented basal cell culture medium or to the complete serum-free eukaryotic cell culture medium comprising said supplemented basal cell culture medium. By using the term "*comprising*", the presence of other (undefined)

ingredients is not excluded and these additional ingredients might well confer properties on the claimed complete serum-free eukaryotic cell culture medium different from those defining the supplemented basal cell culture medium. There is no requirement at all in claim 15 for the claimed complete serum-free eukaryotic cell culture medium to prevent (without promoting or inducing) ESC differentiation.

6.3 According to dependent claim 18, the range of final concentration of the serum-free, eukaryotic culture medium supplement in the complete serum-free eukaryotic culture medium of claim 15 may be as low as "*about 0.5%*" and as high as "*about 90%*". The actual contribution of a medium supplement at such a low final concentration to the desired effect (supporting ESC growth and preventing ESC differentiation) is at least questionable whereas, when at the highest concentration, it is more a (basal) cell culture medium than a medium supplement. This broad range of concentrations blurs any possible technical distinction between supplement and medium and only makes more evident the interdependency between both products to achieve the desired effect (cf. points 4, 6.1 and 6.2 *supra*). Moreover, apart from Example 1 which refers to a 15% final concentration of the supplement, there is no example in the application as filed using any other concentration and certainly not the lowest or the highest ones indicated in claim 18. The term "*about*" introduces further ambiguity into the scope of these claims, for example, would it allow concentrations of 0.3%, 0.2%, 91%, 92%, or more or less?

First auxiliary request

7. Whereas the objection regarding the terms "*transferrin substitutes*" and "*insulin substitutes*" is no longer applicable to this request because a specific list of substitutes for both compounds has been introduced (cf. point 5 *supra*), the other objections raised above in respect of the main request under Article 84 EPC still apply fully.

Second, third and fourth auxiliary requests

8. Although claim 1 of these auxiliary requests is no longer directed to a (serum-free, eukaryotic cell culture) medium supplement, it relates to the use of such a medium supplement and therefore, some of the objections raised above in respect of the main request under Article 84 EPC still apply to these auxiliary requests. In particular, the lack of a clear and unambiguous characterization of that medium supplement (cf. point 4 *supra*) and its broad range of final concentration (cf. point 6.3 *supra*). For the second auxiliary request, the objection regarding the terms "*transferrin substitutes*" and "*insulin substitutes*" still applies (cf. point 5 *supra*).

9. Moreover, the feature introduced into claim 1 of all these auxiliary requests, namely "*as a supporter of embryonic stem cell growth which does not promote embryonic stem cell differentiation in a serum free culture medium which is capable of supporting the growth of embryonic stem cells in serum-free culture and comprises in admixture the supplement and a basal medium*", is also considered to be ambiguous. In fact, whereas the serum-free, eukaryotic cell culture medium

supplement is defined as supporting ESC growth and not promoting ESC differentiation in a serum-free culture medium, the latter feature is not required for the serum-free culture medium.

Conclusion on Article 84 EPC

10. For the above reasons, none of the appellant's requests complies with the clarity requirement of Article 84 EPC. Thus, none of the requests can be allowed.

Article 54 EPC
Main request and first, second, third and fourth auxiliary requests

11. In the communication sent with the summons to oral proceedings, the board raised an objection against all requests on file under Article 54 EPC. This objection of lack of novelty has remained unanswered by the appellant which has decided not to attend the oral proceedings (cf. points VII to IX *supra*). However, since none of the requests on file fulfils the requirements of Article 84 EPC (cf. points 3 to 10 *supra*), the board does not see it necessary to assess and decide on the novelty of each of the appellant's requests in detail.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani