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D E C I S I O N
of 1 March 2004

Case Number: T 0583/03 - 3.3.8

Application Number: 97121096.8

Publication Number: 0854193

IPC: C12N 15/86

Language of the proceedings: EN

Title of invention:
Human retroviral packaging cell line

Applicant:
CHIRON CORPORATION

Opponent:
-

Headword:
Human packaging cell line/CHIRON

Relevant legal provisions:
EPC Art. 54

Keyword:
"Novelty (no)"

Decisions cited:
T 0194/84, T 0198/84, T 0279/89

Catchword:
-

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Case Number: T 0583/03 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 1 March 2004

Appellant: CHIRON CORPORATION
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 18 November 2002 refusing European application No. 97121096.8 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julia
M. B. Günzel

Summary of Facts and Submissions

I. The appeal was lodged by the applicant (appellant) against the decision of the examining division whereby the application 97 121 096.8 with the title "Human retroviral packaging cell line" was refused pursuant to Article 97(1) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC). The priority of US 586603 filed on 21 September 1990 was claimed. The application was a divisional application of the earlier application No. 91 919 095.9 (published as international application WO 92/05266) in accordance with Article 76 EPC.

II. The decision under appeal was based on claims 1 to 7 as originally filed. Claim 1 read as follows:

"1. A human retroviral packaging cell line comprising a human host cell line containing a gag/pol gene and an env gene, the cell line being one which upon introduction of a vector construct, is capable of producing vector particles substantially uncontaminated by replication competent virus, with the proviso that said human cells are not T-cells or monocytes which contain gag/pol and env genes derived from the murine amphotropic retrovirus 4070A which has been adapted for growth in said T-cells or monocytes."

Claims 2 to 5 were specific embodiments of claim 1 related to the tropism (amphotropic, polytropic and xenotropic) of the packaging cell line or to the parental cell line (293 or HT1080). Claim 6 concerned a human retroviral producer cell line comprising a human host cell line according to any of claims 1 to 5 and a

gene encoding a retroviral vector. Claim 7 was directed to the human retroviral producer cell line of claim 6 for use in a method of treatment of the human body.

III. The board issued a communication, annexed to the summons to the oral proceedings. With reference to *inter alia* decision T 194/84 (OJ EPO 1990, 59), the board indicated its preliminary, non-binding opinion in respect of novelty and inventive step, which was in line with that of the decision under appeal.

IV. Oral proceedings were held on 1 March 2004.

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

D1: EP-A-0 386 882 (published on 12 September 1990);

D2: EP-A-0 334 301 (published on 27 September 1989);

D3: declaration of Dr DePolo (dated 30 June 1995).

VI. Appellant's arguments in writing and during oral proceedings insofar as they relate to the present decision may be summarized as follows:

Article 54 EPC

As illustrated by Dr DePolo in his declaration (document D3) with reference to the prior art, in the literature it was assumed that the clearance rate of a retrovirus in human serum was related to the specific viral envelope - env - glycoprotein present in the retroviral virion. The technical contribution of the

application was the finding that this clearance rate was actually related to the packaging cell's membrane in which was embedded the viral env glycoprotein. When using human cell lines in preference to any other cell line as packaging cell lines, the resulting virions had a lower clearance rate in human serum, i.e. the virions packaged in human cell lines were more resistant to inactivation by antibody independent complement lysis in human serum - as shown in Table I of document D3. The prior art taught at most, generically, that any cell line could be used as a packaging cell line, whereas the subject-matter of claim 1 specified that the packaging cells should be **human**.

Although document D1 mentioned also human cell lines which could be used, this was in the context of a list of specific other cells of differing species and of a preceding statement that virtually any cell line could be used. Document D1 was a generic disclosure of virtually any cell line and, at a second level, of any mammalian cell line. The reference to four specific human cell lines had to be seen in this context. These human cell lines were well-known, stable cell lines like the other non-human cell lines mentioned in the same sentence (CV-1 and CHO), i.e. they were the standard cell lines, so to say, "the nuts and bolts", used for recombinant expression in mammalian cells. All of these cell lines were only cited for this very specific reason and without emphasizing any particular advantageous property associated to the fact that they were human. Document D1 did not make the skilled person aware of any specific advantageous effect in using human cell lines over other mammalian cell lines. On reading document D1, the skilled person would

understand that any mammalian cell line could be used, in particular well-known standard cell lines. However, for the reasons set out in document D3, there were distinct advantages in selecting human cell lines over other cell lines, in particular an increased resistance to human serum. Thus, the reference in document D1 to four specific human cell lines could not be seen as an implicit generic disclosure of human cell lines. Such an intermediate generalization was not, as required by the established case law of the Boards of Appeal, directly and unambiguously derivable from the teachings of document D1 as a whole.

In line with the established case law concerned with the novelty of selection inventions, developed in decision T 198/84 (OJ EPO 1985, 209) and summarized in decision T 279/89 of 3 July 1991, claim 1 represented: (i) a narrow selection as it was directed to a human cell, whereas the prior art specified virtually any cell type, (ii) a selection far removed from the preferred part of the known examples which used COS-1 monkey cells and (iii) a selection which was not arbitrary but purposive as shown by the advantages referred to in document D3. Document D1 emphasized the selection of particular vector sequences and not the type of host cell itself, let alone that the cell line was important in the effectiveness of the vector. Similarly, document D2 was centred on the choice of the vector and not on the choice of the host cell. Since there was no suggestion in either document D1 or D2 that human packaging cells should be preferred to other types of cells, the claims were inventive over the combined teachings of said documents.

VII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims as originally filed.

Reasons for the Decision

Article 54 EPC (Novelty)

1. With the final goal - as the present application - of establishing a "safe" gene transfer system, document D1 discloses human retroviral packaging cell lines comprising a human host cell line containing a gag/pol and an env gene, the cell line being one which upon introduction of a vector construct, is capable of producing vector particles substantially uncontaminated by replication competent virus. In particular, document D1 identifies the HIV packaging sequence and discloses vectors comprising HIV gene products but without the HIV packaging signal. These vectors are used to transform preselected cell lines which result in HIV packaging cell lines. A preferred embodiment comprises the transformation of a cell line using at least two vectors, which collectively contain the HIV nucleotides necessary to express HIV gag, pol, and env products, but wherein each vector does not contain the HIV nucleotides necessary to express all three products. Moreover, none of these vectors contains the HIV packaging sequence and each vector contains a different marker gene (cf. column 3, line 47 to column 4, line 8). It is further preferred that these packaging cell lines do not produce any infectious HIV and therefore, HIV nucleotide segments that do not correspond to the entire HIV genome are used (cf. column 5, lines 34

to 52). When a further vector comprising the HIV packaging sequence and a predetermined gene transfects these HIV packaging cells, the nucleotide sequence from this vector will be packaged in the virions and these "HIV packaged" genes can be targeted to cells infectable by HIV (cf. column 7, lines 25 to 52).

2. The teachings of document D1 are exemplified using COS-1 cells from African green monkey (cf. column 8, line 2 to column 10, line 1). However, column 6, lines 32 to 34 reads "*Virtually any cell line can be used. Preferably, one would use a mammalian cell line, for example, CV-1, Hela, Raji, RD, SW480 or CHO cell lines*", wherein Hela, Raji, RD and SW480 are human cell lines known from the prior art. Thus, document D1 discloses four specific human retroviral packaging cell lines comprising a human host cell line containing a gag/pol gene and an env gene, the cell line being one which upon introduction of a vector construct, is capable of producing vector particles substantially uncontaminated by replication competent virus. It is well established case law of the Boards of Appeal that, whereas a generic disclosure does not normally take away the novelty of a specific claimed embodiment, the disclosure of a specific embodiment takes away the novelty of a generic claim (cf. "Case Law of the Boards of Appeal of the European Patent Office", 4th edition 2001, I.C.3.2.6, page 72). Thus, document D1 is considered to anticipate the subject-matter of claim 1.

3. It is also established case law of the Boards of Appeal that for the purpose of novelty the teachings of a prior art document are not necessarily confined to the specific working examples disclosed therein but they

also comprise anything that is directly and unambiguously derivable from that document including any possible implicit teaching in the document as a whole (cf. "Case Law" *supra*, I.C.2.7, 60). A disclosure of one or more specific embodiments can be regarded as implicitly disclosing a more general term if it is clear to the skilled person that its teaching is also applicable to other embodiments falling under the more general term (cf. *inter alia* T 194/84, OJ EPO 1990, 59, points 2.3 and 2.4 of the Reasons, where this was examined under Article 123(2) EPC but eventually denied).

4. As stated in point 2 above, document D1 reads "*virtually any cell line can be used*" (cf. column 6, line 32). However, it immediately indicates that "***preferably**, one would use a mammalian cell line, **for example**, CV-1, Hela, Raji, RD, SW480 or CHO cell lines*" (emphasis by the board). Thus, from the first broad generic group of possible packaging cell lines, a preferred subgroup, mammalian cell lines, is explicitly highlighted and within this subgroup six specific examples are also indicated. In line with the general context of this sentence, these examples are understood as preferred mammalian cell lines. In fact, document D1 suggests - in order to increase the production of viral cellular products - to replace the 5' LTR with a promoter that preferentially expresses genes in the particular cell line used and, as a specific example, it refers to the CMV promoter suitable for CV-1 and Hela cell lines (cf. column 6, lines 35 to 41), i.e. the first and second cell lines mentioned as preferred cell lines. The relevance of these cell lines is further emphasized by the fact that the cell line used

in the working example, COS-1, is directly derived from the CV-1 cell line (from the African green monkey Cercopithecus aethiops).

5. The said preferred mammalian cell lines are derived from three different species, namely African green monkey (CV-1), Chinese hamster (CHO) and human (Hela, Raji, RD and SW480). However, whereas for each of the first two species only one cell line is mentioned, four cell lines are indicated for human. Thus, the relevance of human cell lines is immediately recognized alone from the sheer number of human cell lines explicitly mentioned in document D1: four out of six.

6. It has been argued by the appellant that the cell lines indicated in document D1 are all well-known, standard cell lines normally used for the expression of recombinant products in mammalian cells. In its view, they are a mere recitation of basic elements - "the nuts and bolts" - of recombinant expression in mammalian cells and they only convey to the reader the information to use any possible known and available mammalian cell line. This interpretation does not, however, change the fact that four out of six (standard) cell lines mentioned in the document as envisaged host cell lines are **human**. The reader would also assume that other human standard cell lines, such as for e.g. human cell lines WI-38 and 293 (cf. column 7, lines 37 to 51 and column 36, lines 36 to 42, respectively, in document D2), would be useful as host cells.

7. Thus, the board concludes from the foregoing that the teachings of document D1 are not confined to the specific cell lines and working examples disclosed

therein but they also comprise as an additional implicit teaching the use of human cell lines as HIV packaging mammalian cell lines (cf. point 3 *supra*).

8. In view of the conclusions reached in point 7 above, the board does not consider that the principles applied by the Boards of Appeal as part of their established case law on the novelty of selection inventions, in particular for a selection of a sub-range from a broader range, as developed in decision T 198/84 (cf. *supra*) and summarized in decision T 279/89 (cf. *supra*), are applicable in the present case (cf. also "Case Law", supra, I.C.4.2.1, 80). As it has been said, the alleged sub-range is itself already disclosed in document D1 - albeit in an implicit manner. Moreover, in the light of the four specific human cell lines disclosed in document D1, a sub-range directed to general human cell lines could not be seen as narrow or, even less, sufficiently far removed from the preferred part of the known range. It is also worth noting at this point that the specific effect on which the alleged purposive selection is based, namely the lower clearance rate of human packaging cell lines in human serum, is not disclosed in the application as filed but only in the expert declaration of Dr DePolo (document D3).

9. It follows from all the foregoing, that the claimed subject-matter, and consequently the present request that comprises this subject-matter, does not fulfil the requirements of Article 54 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani