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Datasheet for the decision of 7 December 2006

Case Number: T 0472/06 - 3.3.08

Application Number: 97954089.5

Publication Number: 0948614

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Novel expression vectors containing accessory molecule ligand genes and their use for immunomodulation and treatment of malignancies and autoimmune disease

Applicant:
University of California

Opponent:
-

Headword:
Ligand genes/CALIFORNIA

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request: inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0472/06 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 7 December 2006

Appellant: University of California
Technology Transfer Office
Mail code: 0093
9500 Gilman Drive
La Jolla, CA 92093-0093 (US)

Representative: Viering, Jentschura & Partner
Postfach 22 14 43
D-80504 München (DE)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 15 November 2005 refusing European application No. 97954089.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division dated 15 November 2005, whereby the European patent application No. 97 954 089.5 with publication number 0 948 614 was refused. The application, entitled "*Novel expression vectors containing accessory molecule ligand genes and their use for immunomodulation and treatment of malignancies and autoimmune disease*", originated from an International application published as WO 98/26061 (which will be referred to in the present decision as the "application" or the "application as filed").

II. The application had been refused for reason of non-compliance with the requirements of Article 56 EPC, the basis for the refusal being the main request filed on 13 September 2005. The examining division found that the application did not provide any evidence that the underlying problem formulated on the basis of the closest state of the art (cf. document D3 or D4; see *infra*), i.e. providing improved CD40 ligands stable on the cell surface, was actually solved. Example 2, although giving experimental protocols, did not describe an experiment which had been performed. Later document D6 filed in support of inventive step showed that a specific design of chimeric molecules was necessary which was different from the one considered in the application.

III. Together with the statement setting out the grounds of appeal dated 16 March 2006 the appellant submitted a first auxiliary request and two documents with experimental data.

IV. The examining division did not rectify its decision and referred the appeal to the Board of Appeal (Article 109 EPC).

V. On 8 September 2006 a communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal presenting some preliminary and non-binding views of the Board was sent to the appellant.

VI. In reply to that communication, the appellant filed observations in a letter dated 6 November 2006, which was accompanied by a new main request to replace the previous one and an expert opinion of Ms Arnhild Schrage.

VII. Oral proceedings took place on 7 December 2006, at which the appellant filed a new main request to replace that on file.

VIII. The **main request of 7 December 2006** consisted of 21 claims.

Claim 1 read:

"1. A chimeric CD40 ligand gene consisting of nucleotide sequences encoding domains in the following order: a cytoplasmic domain (Domain I), a transmembrane domain (Domain II), a proximal extracellular domain (Domain III) and a distal extracellular domain (Domain IV), characterized in that at least one of said domains is derived from a murine CD40 ligand gene and the other domains are derived from a human CD40 ligand gene."

Claim 2 read:

"2. A chimeric CD40 ligand gene consisting of nucleotide sequences encoding domains in the following order: a cytoplasmic domain (Domain I), a transmembrane domain (Domain II), a proximal extracellular domain (Domain III) and a distal extracellular domain (Domain IV), characterized in either
a) Domains III and IV are derived from a human CD40 ligand gene and Domains II and I are derived from a murine CD40 ligand gene, or
b) Domains III and IV are derived from a murine CD40 ligand gene and Domains II and I are derived from a human CD40 ligand gene, or
c) Domains II, III and IV are derived from a human CD40 ligand gene and Domain I is derived from a murine CD40 ligand gene, or
d) Domains II, III and IV are derived from a murine CD40 ligand gene and Domain I is derived from a human CD40 ligand gene, or
e) Domains I, III and IV are derived from a human CD40 ligand gene and Domain II is derived from a murine CD40 ligand gene, or
f) Domain III is derived from a murine CD40 ligand gene and Domains I, II and IV are derived from a human CD40 ligand gene."

Claim 3 was dependent on claim 2 and directed to six particular CD40 ligand genes. Claim 4 was dependent on claim 1 or 2 and directed to a CD40 ligand gene wherein the protease cleavage site(s) of nucleotide sequences of domain III has/have been removed. Claim 5 was dependent on any of claims 1 to 4 and directed to a

CD40 ligand gene wherein said gene was operably linked to a promotor region and a polyadenylation signal.

Claim 6 was directed to a vector comprising a chimeric CD40 ligand gene of any of claims 1 to 5. Claim 7 was dependent on claim 6 and directed to a particular embodiment thereof.

Claim 8 was directed to a host cell comprising a nucleotide sequence or a vector as defined in any of claims 1 to 7. Claims 9 to 11 were dependent on claim 8 and directed to particular embodiments thereof.

Claim 12 was directed to a pharmaceutical composition comprising a chimeric CD40 ligand gene or a vector as defined in any of claims 1 to 7. Claims 14 and 15 were dependent on claim 12 and directed to particular embodiments thereof.

Claim 13 was directed to a pharmaceutical composition comprising a host cell as defined in any of claims 8 to 11.

Claim 16 was dependent on claims 12 to 15 and directed to particular embodiments thereof.

Claim 17 was directed to the use of a chimeric CD40 ligand or a vector as defined in any of claims 1 to 7 for the manufacture of a medicament for the treatment of neoplasia. Claims 18 and 19 were dependent on claim 17 and directed to particular embodiments thereof.

Claim 20 was directed to a polypeptide encoded by a nucleotide sequence or a vector as defined in any of claims 1 to 7.

Claim 21 was directed to an *in vitro* method of altering the immunoreactivity of human cells comprising introducing a chimeric CD40 ligand gene or a vector as defined in any of claims 1 to 7 into said human cells so that said chimeric CD40 ligand was expressed on the surface of said cells.

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

(D3) WO 95/14487 (published on 1 June 1995)

(D4) WO 94/17196 (published on 4 August 1994)

(D6) WO 03/099340 (published on 4 December 2003)

X. The submissions made by the appellant, insofar as they are relevant to the decision, may be summarised as follows:

Inventive step (Article 56 EPC)

In the state of the art (see document D4), it was proposed to use soluble human CD40 ligand to stimulate the immune system. However, soluble human CD40 ligand was not optimal for cross-linking the human CD40 molecules on antigen presenting cells and did not work as effectively as CD40 ligands expressed on a cell membrane to produce strong stimulation of antigen presenting cells.

The technical problem was regarded as the provision of CD40 ligands susceptible of being stably expressed on the surface of human antigen presenting cells as a way to stimulate the immune system.

The provision of chimeric human/murine CD40 ligands as defined in claim 1 represented a plausible solution to that problem.

For a complete assessment of the experiments carried out by the appellant which led it, following a logical chain of reasoning, to formulate the inventive concept underlying the invention, not only Example 2 in the application should be taken into consideration but also Example 1 with its detailed results (see in particular pages 61 to 64 as well as Figures 3, 8 and 9). It was shown that the human CD40 ligand failed to be expressed on the surface of the human CLL cells, whereas the murine CD40 ligand was expressed (see page 62, lines 6 to 20, together with Figure 3). Furthermore, it was also established that T cells of patients with CLL did not express detectable human CD40 ligand after CD3 ligation and that, although both human CD40 ligand and human CD40 ligand RNA were expressed in normal donor T cells, the levels of neither the protein nor the RNA were stably maintained (see page 64, lines 6 to 24, together with Figures 8 and 9).

Figure 9 of later document D6 showed that a chimeric molecule such as ISF5, which consisted of murine and human domains, could be expressed with improved stability on the surface of CLL B cells which normally

did not express these molecules in sufficient amounts to allow an effective activation of the immune system.

As there was no evidence in the state of the art, as represented by documents D3 and D4, to suggest that the proposed chimeric ligands were obvious, the presence of an inventive step should be acknowledged.

XI. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request filed during the oral proceedings.

Reasons for the Decision

Main request

Requirements of Article 123(2) EPC

1. The Board is satisfied that the requirements of Article 123(2) EPC are met.

1.1 In particular, support exits in the application as filed: (i) on page 30, lines 1 to 12, and page 31, lines 32 to 36 for claim 1, (ii) from line 30 on page 30 to line 31 on page 31 and on page 34, lines 3 to 9 for claims 2 and 3, (iii) from line 26 on page 32 to line 15 on page 33 for claim 4, (iv) on page 39, lines 27 to 33 for claim 5, (v) on page 43, lines 13 to 26 for claim 13, (vi) on page 54, lines 9 to 16 for claim 15, and (vii) in claim 83 together with page 19, lines 11 to 24 and page 74, lines 27 to 32 for claim 21.

1.2 The same conclusion applies also to all the remaining claims in respect of which the Board confirms the positive conclusion expressed by the examining division in the decision under appeal.

Clarity requirement of Article 84 EPC

2. The Board is of the view that, with the amendments introduced into the claims, which correctly identify the component parts of the claimed chimeric ligand gene, the main request now defines the matter for which protection is sought in a clear and unambiguous manner.

Inventive step (Article 56 EPC)

3. The present invention relies on the concept that cells which normally do not express the human CD40 ligand are capable of stably expressing on their surface chimeric human/murine CD40 ligands and the subsequent idea of using a gene encoding such a ligand as the active ingredient in the preparation of a medicament for the treatment of a neoplasia or as a means to perform an *in vitro* method of altering the immunoreactivity of human cells.

4. The basic question to be assessed in the present case is whether a person skilled in the art would have regarded such a concept as obvious in view of the state of the art.

5. As regards CD40 ligands, two documents representing the state of the art cited in the examination proceedings are to be considered, namely documents D3 and D4. While document D3 discloses that the human CD40 ligand, in

soluble, monomeric, dimeric or oligomeric form, is useful upon administration in the prophylactic or therapeutic treatment of a virus infection in a human or an animal, document D4 teaches "a method of treating an individual that has a syndrome in which the interaction of T cells and B cells is affected", that method comprising administering a soluble human CD40 ligand (see page 2, lines 32 to 34).

6. Therefore, at the priority date the relevant state of the art was pointing to the use of human CD40 ligand, or derivatives thereof, as the active ingredient of a pharmaceutical composition in the treatment of some diseases. The capability of human cells to express the murine CD40 ligand had not been yet recognised. Nor had it been observed that neoplastic human cells such as CLL cells lack human CD40 ligand surface expression. Thus, there is no doubt that at the priority date the concept on which the present invention relies would have been **unobvious** to the skilled person.

7. A further question to be answered is whether it may be considered that the concept may plausibly find application in the light of the available technical information contained in the application as filed, possibly supplemented by the later evidence.

8. The examining division in its decision held that the application provided no evidence that the expected technical effect associated with the use of a chimeric human/murine CD40 ligand gene had actually been achieved, the reason being that it was not credible that the experiments described in Example 2 (see pages 76 to 79 in the application) had been performed. Not

only were results announced without any detailed support but also the use of the present tense was proof that the experiments described were only suggested and had not actually been performed.

9. Although particular attention has to be paid to Example 2 (see pages 76 to 79) which is the only place in the application as filed which describes experiments involving chimeric CD40 ligand genes according to claim 1, the Board is convinced that looking at only Example 2 would lead inescapably to a limited understanding of the situation of the applicant which was faced, at the time the invention was made, with largely uncharted territory and which derived *ex-nihilo* the concept underlying the claimed invention.

10. Looking at Example 1 (see pages 59 to 76 in the application) shows indeed preliminary detailed results which paved the way for the invention. There is in particular the demonstration of paramount importance that the human CD40 ligand fails whereas the murine CD40 ligand succeeds to be expressed on the surface of human CLL cells transfected with a vector carrying the corresponding CD40 ligand gene (see page 62, lines 5 to 20, together with Figure 3), the expression of the murine CD40 ligand being moreover persistent (see page 64, lines 13 to 24, together with Figure 9). There is also the essential demonstration that human CLL cells containing the murine CD40 ligand genes are effective in producing an enhanced immune response (see pages 70 to 71). These are the results which led the appellant to follow a logical chain of reasoning resulting in the concept that replacing in the human CD40 ligand gene one or more domains with the

corresponding domain(s) in the murine CD40 ligand gene would permit the resulting chimeric CD40 ligand to be stably expressed on the surface of human neoplastic cells such as CLL cells upon transfection with a vector encoding the chimeric gene.

11. Example 2 describes precisely the preparation of six particular chimeric human/murine CD40 ligand genes and their expression in human CLL cells. The gene constructs which have been tested are clearly identified (see page 77, lines 23 to 27 and page 79, lines 2 to 10). These are the nucleotide sequences with the sequence identifiers SEQ ID NOs: 3 to 7 and 20 (see claim 3). The FACS analysis which has been carried out is also specified (see page 77, lines 30 to 32). However, no detailed experimental results are given. Only statements are made indicating that (i) after appropriate analysis and preparation of appropriate histograms, the expression of the chimeric CD40 ligand genes is confirmed (see page 78, lines 2 to 5, and page 79, lines 17 to 20), (ii) increased amounts of CD54 and CD80 are found on cells containing such a ligand gene (see page 78, lines 16 to 19, and page 79, lines 20 to 23), and (iii) those cells are able to stimulate the production of gamma interferon and T-cell proliferation.

12. Use of the present tense apart, the Board sees no reason to question whether the experiments described in Example 2 have been actually performed. Nevertheless, it remains to be assessed whether the results of Example 2 are plausible in view of later document D6, which was also relied on by the examining division in its negative conclusion.

13. Document D6 is a post-published document submitted by the appellant itself in support of its case and to be seen as an expert opinion. The polynucleotide sequences described in document D6 encode chimeric CD40 ligands in which one or more **subdomain(s)** is/are of a **non-human** origin, preferably of a **murine** origin, and the other **subdomain(s)** is/are of a **human** origin (see in particular paragraph 00110 on pages 22 to 23 and claim 1). Such chimeric genes are not encompassed by claim 1 of the main request. Thus, any conclusion drawn regarding such chimeric genes of document D6 is meaningless with respect to the present assessment. Two chimeric CD40 ligands encoded by genes, which have been acknowledged by the appellant to be encompassed by claim 1 of the main request (see top of page 4 of the statement setting out the grounds of appeal), have been included in some experiments reported in document D6. The results of those experiments are given in the form of histograms which confirm that, as announced in Example 2 of the present application, human CLL cells transfected with a vector carrying a chimeric CD40 ligand gene according to claim 1 are indeed capable of expressing the encoded chimeric CD40 ligand. Therefore, the plausibility of the results of Example 2 of the application cannot be questioned on the basis of document D6.

14. Thus, in view of the above remarks, the Board concludes that the claimed invention as a whole involves an inventive step. Therefore, the main request meets the requirements of Article 56 EPC.

15. As the Board is satisfied that the other requirements of the EPC are also meet, the main request may form a basis for the grant of a patent.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of claims 1 to 21 of the main request filed during the oral proceedings and a description and drawings to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski L. Galligani