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# D E C I S I O N
## of 8 December 2005

**Case Number:** T 1306/04 - 3.3.08

**Application Number:** 95102829.9

**Publication Number:** 0670369

**IPC:** C12N 15/12

**Language of the proceedings:** EN

**Title of invention:**
A novel peptide related to human programmed cell death and DNA encoding it

**Applicants:**
ONO PHARMACEUTICAL CO., LTD.
Honjo, Tasuku

**Opponent:**
-

**Headword:**
Cell death peptide/ONO

**Relevant legal provisions:**
EPC Art. 56

**Keyword:**
"Claim 1: inventive step (no)"

**Decisions cited:**
T 1329/04

**Catchword:**
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 1306/04 - 3.3.08

# D E C I S I O N
**of the Technical Board of Appeal 3.3.08**
**of 8 December 2005**

**Appellants:** (Opponents)
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**Representative:**
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**Decision under appeal:** **Decision of the Examining Division of the European Patent Office posted 28 May 2004 refusing European application No. 95102829.9 pursuant to Article 97(1) EPC.**

**Composition of the Board:**

**Chairman:** F. Davison-Brunel
**Members:** T. J. H. Mennessier
B. Günzel

## Summary of Facts and Submissions

I. The applicants (appellants) lodged an appeal against the decision of the examining division of 28 May 2004 refusing the European patent application No. 95 102 829.9, entitled "A novel peptide related to human programmed cell death and DNA encoding it", with publication number 0 670 369.

II. Reason for the refusal was lack of inventive step (Article 56 EPC) over the combined teachings of documents D1 and D2 (see paragraph IX infra) of the request (claims 1 to 16) filed on 5 March 2004.

III. Together with their statement of grounds of appeal the appellants filed two additional documents in support of their view that the request of 5 March 2004 was inventive.

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

V. 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 appellants.

VI. In reply to the Board's communication, on 8 November 2005, the appellants submitted a new main request (claims 1 to 14) to replace the request on file, together with observations accompanied by two further documents.

VII. Claim 1 of the main request read as follows:

"1. A polypeptide in substantially purified form having the amino acid sequence shown in SEQ. ID. No. 1 or amino acid sequence having at least 90 % homology with the amino acid sequence shown in SEQ. ID. No. 1."

VIII. Oral proceedings took place on 8 December 2005.

IX. The following documents are cited in the present decision:

(A) One page document submitted at the oral proceedings before the examining division on 6 April 2004 as Reference 3 (dated 28 March 2004);

(B) Pages 1049 to 1051 of a document in the Japanese language submitted at the oral proceedings before the examining division on 6 April 2004 as Reference 2 (dated "2000. 3. 4");

(D1) Yasumasa Ishida et al., J. EMBO, Vol. 11, No. 11, 1992, Pages 3887 to 3895;

(D2) Database WPI, Section Ch, Week 9404, Derwent Publications Ltd., London, GB; Derwent Classes B04 and D16, AN 94-030912; Derwent abstract in the English language of the Japanese application JP-A-05-336973 (published on 21 December 1993);

(D4) Ludmila Prokunina et al., Nature Genetics, Vol. 32, December 2002, Pages 666 to 669;

(D6) Automatically processed translation in the English language of the Japanese patent application JP-A-05-336973 (published on 21 December 1993).

X. Insofar as relevant to the present decision the submissions of the appellants in writing and during oral proceedings may be summarised as follows:

Inventive step (claim 1)

The closest prior art was document D1 which described the cloning of a DNA encoding the mouse PD-1 protein. Document A showed that PD-1 contained an ITIM-motif and that not each and every protein comprising such a motif could be found at the same time in the human being and all tested rodent species. On the contrary, they were rather seen only in the mouse and the rat, or only in the mouse and the human being or even only in the mouse. This latter situation applied, for example, to protein gp49B as indicated in document B.

In view of those documents, at the priority date one skilled in the art could not reasonably expect that a human homologue of the murine PD1-1 protein would exist.

For this reason alone the protein of claim 1, which comprised an ITIM motif, was inventive.

A further argument in favour of the notion that there was no certainty that an homologue to a mouse protein would be found in the human being was that, as disclosed in 2002, the proportion of mouse genes with a single identifiable orthologue in the human genome

seemed only to be approximately 80% and that the proportion of mouse genes without any homologue detectable in the human genome (and vice versa) seemed to be less than 1%.

In addition, the fact that only one out of seven human cell lines had been found capable of expressing PD-1 mRNA (see Example 2 in the patent application) and that, as reported in post-published documents, the human PD-1 DNA had been proved to be useful in the diagnosis of systemic lupus erythematosus in humans were also indicia of inventive step.

XI. The appellants requested that the decision of the examining division be set aside and a patent be granted on the basis of the claims filed with the letter dated 8 November 2005.

## Reasons for the Decision

1. The key issue to be decided is whether the subject-matter of claim 1 involves an inventive step in the light of the state of the art.

2. This claim is concerned with a polypeptide, designated as "human PD-1" (see page 2, lines 52 and 53 in the application as published), having a definite amino acid sequence as represented in the sequence identifier SEQ. ID. No. 1, the encoding cDNA of which has been isolated from a human cell line.

3. Document D1 is considered to represent the closest state of the art. It describes the activation of a cell death-associated gene, termed PD-1, in two **murine** lymphoid cell lines (2B4.11 and LyD9) and the isolation of a cDNA clone from a cDNA library prepared from stimulated 2B4.11 cells. Figure 2 shows the structure of this cDNA and the predicted amino acid sequence of the corresponding protein, ie the **murine** PD-1 protein.

4. In view of document D1, the technical problem to be solved is regarded as the provision from an organism other than the mouse of a protein homologue to the murine PD-1 protein. The solution to this problem is represented by the protein of claim 1 which is the **human** PD-1 protein.

5. The first question to be answered is whether the skilled person would have found in the state of the art any incentive to look for an homologue of the murine PD-1 protein in animals other than the mouse and more particularly in the human being.

6. Document D2 is an English abstract of the Japanese patent application JP-A-05-336973. It contains the indication that human PD-1 and a DNA encoding the same are claimed in that application. This is confirmed in document D6 which is an automatic translation of the application JP-A-05-336973 provided by the Japanese patent office. Whereas document D6, which was submitted by the appellant at the oral proceedings held before the examining division, is not a certified translation and, therefore, may not precisely reflect the content of the original document as filed in the Japanese language, it is not doubtful that it discloses the

murine PD1-protein (see the amino acid sequence in paragraph 0060 on pages 13/17 and 14/17) and contains the indication of the existence in Homo sapiens of a protein having a high homology therewith (see the sentence bridging pages 3/17 and 4/17 and the mentioning of claims 7 and 8 on page 1/1). The Board is therefore of the opinion that a reading of documents D2 or D6 would have prompted the skilled person to decide to investigate cell lines of **human origin** for the presence of the announced homologue of the murine PD-1 protein.

7. The appellants argued that the skilled person would not have regarded it as credible that an homologue of the murine PD-1 protein could exist in the human being, as it was well-known at the priority date that the inhibitory signal transmission molecular group of murine proteins, to which murine PD-1 protein belonged, were encoded by a lot of genes without any counterpart in the human genome. In support of their views the appellants submitted documents A and B. Document A is an excerpt from an internet site which was retrieved on **28 March 2004**. This excerpt contains only a figure without any legend. In the figure proteins with an ITIM motif are schematically represented with the indication of their presence in (i) both the human being and the mouse, (ii) the human being only, (iii) bovine animals only, (iv) the rat only, (v) the mouse only or (vi) both the mouse and the rat. **The PD-1 protein is shown to be present in both the human being and the mouse**. Therefore, document A speaks out against the appellants' position. Document B is written in Japanese, i.e. in a language which is not one of the official languages of the EPO. According to a hand-written

English mention (see page 1049), it should be an article post-published in a scientific journal. It contains an hand-written non-certified translation (see page 1051) of a passage in which it would appear to be reported that no homologue of the (murine) gp49B protein (also represented in document A) has been found in the human being. In view of the extremely poor quality of this piece of evidence, the Board decides not to take it into account for the present assessment.

8. The submission made at the oral proceedings that it was known from 2002 onwards that the proportion of mouse genes with a single identifiable orthologue in the human genome seemed to be approximately 80% and that **the proportion of mouse genes without any homologue detectable in the human genome (and vice versa) seemed to be less than 1%**, if to be taken into account at all, does not speak in favour of a lack of reasonable expectation of success when cloning the human PD-1 cDNA.

9. The next question to be answered is whether the skilled person would have encountered any special difficulty in his/her investigation when looking for an homologue of the murine PD-1 protein in the human being.

10. In their written submissions the appellants raised the argument that the inventors were able to isolate a cDNA encoding a PD-1 protein from only one out of seven human cell lines tested (see Examples 1 to 4 on page 7 in the application) and that this was a sign that the skilled person could not have obtained it with only routine experimentation.

11. Yet, the skilled person would have learnt from document D1 that more than one cell line should be tested and that lymphoid cell lines were appropriate candidates to perform his/her investigation. A number of human lymphoid cell lines were available to the public at the priority date (see Example 1 in the patent application). Choosing seven of them at random (as is derivable from the application in which no criteria of selection are mentioned) cannot be regarded as a difficult task, no more than testing the RNA produced by those cell lines for its ability to bind mouse PD-1 DNA. Moreover, the Board notices that there is no indication in Example 2 that a satisfactory hybridization signal was observed only from YTC3 RNA and not from the RNAs produced by the six other tested cell lines.

12. In fact, the appellants did not point out that the cloning of the gene encoding the human PD-1 protein was associated with any unusual problem.

13. The last argument presented in favour of inventive step was that the beneficial use of the human PD-1 cDNA in the diagnosis of systemic lupus erythomatosus was an unexpected advantage. Unfortunately, the application makes no mention of this specific use for which evidence was seemingly obtained some eight years after the priority date (see document D4). In fact, the only passage in the patent specification relating to use consists in a very general statement on page 10, lines 16 to 20. Here, the appellants are reminded of the case law of the Boards of Appeal (see, in particular, T 1329/04 of 28 June 2005, point 12 of the reasons) relating to the unsuitability, when assessing inventive step, of taking post-published documents into

consideration if the effect taught in these documents is not made at least plausible in the patent application *per se*. In accordance with this case law, the Board does not consider the argument to be convincing.

14. Taking into account the remarks made in points 1 to 13 supra, the Board comes to the conclusion that the subject-matter of claim 1 does not involve an inventive step, thereby failing to comply with the requirements of Article 56 EPC. Thus, the main and sole request is rejected.

## Order

## For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski F. Davison-Brunel