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Datasheet for the decision of 12 June 2008

Case Number: T 1805/06 - 3.3.08

Application Number: 95934477.1

Publication Number: 0784687

IPC: C12N 15/53

Language of the proceedings: EN

Title of invention:
Cloning and expression of cDNA for human dihydropyrimidine dehydrogenase

Applicant:
The United States of America, as represented by the Secretary of the Department of Health and Human Services

Headword:
DPD Sequence/UNITED STATES

Relevant legal provisions:
EPC Art. 123(2)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request and auxiliary request - added subject-matter (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1805/06 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 12 June 2008

Appellant: THE UNITED STATES OF AMERICA, as represented by the Secretary of the Department of Health and Human Services
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 17 July 2006 refusing European application No. 95934477.1 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
B. Günzel

Summary of Facts and Submissions

I. European patent application No. 95 934 477.1, published as International patent application WO 96/08568 with the title "Cloning and expression of cDNA for human dihydropyrimidine dehydrogenase" (referred to as "the application as filed" hereinafter), was refused pursuant to Article 97(1) EPC 1973.

II. The examining division considered that the application did not fulfil the requirements of Articles 123(2), 84, 52 and 56 EPC. In particular, an amended "Sequence Listing" was considered to contravene Article 123(2) EPC since the length of the nucleic acid sequence of Seq. ID. No. 15 of this "Sequence Listing" was different from the length of the corresponding nucleic acid sequence in the application as filed (Figure 1). The examining division also identified several inconsistencies between the nucleic acid sequences of Seq. ID. No. 1 and Figure 1 of the application as filed (Article 84 EPC).

III. The applicant (appellant) filed an appeal against the decision of the examining division and paid the appeal fee. On 21 November 2006, the appellant filed a statement setting out the grounds of appeal together with an amended set of claims (Annex 1) and a new amended "Sequence Listing" (Annex 2).

IV. The examining division did not rectify the contested decision and referred the appeal to the board of appeal (Article 109 EPC 1973).

V. The board sent a communication, as annex to the summons to oral proceedings, stating its preliminary, non-binding opinion on formal and substantive matters. In particular, the appellant was informed that, in the light of the differences between the nucleic acid sequences of Seq. ID. Nos. 15 and 16 of the amended "Sequence Listing" and the corresponding nucleic acid sequences of the application as filed, the amended "Sequence Listing" (Annex 2 in appellant's grounds of appeal) did not appear to fulfil the requirements of Article 123(2) EPC.

VI. On 12 May 2008, the appellant replied to the board's communication and filed a new main request and an auxiliary request.

VII. On 3 June 2008, as a reply to appellant's inquiries, the board sent a fax to the appellant indicating its preliminary opinion on the requests then on file. The appellant was informed thereby that these requests did not appear to overcome the objections raised in the board's communication under Articles 123(2), 84 and 56 EPC. Oral proceedings were maintained as scheduled.

VIII. With a fax dated 11 June 2008 the appellant informed the board that it did no longer wish to attend the oral proceedings, that the request for oral proceedings was cancelled and that a decision of the board in writing was requested.

IX. Nevertheless, in order to reach a decision in the case, the board decided to continue with the oral proceedings which took place, in the absence of the appellant, on 12 June 2008.

X. Claims 1 and 6 of the **main request** read as follows:

"1. An isolated nucleic acid encoding a dihydropyrimidine dehydrogenase (DPD) protein, said nucleic acid capable of selectively hybridizing to a second nucleic acid consisting of the nucleotide sequence of Seq. ID. No. 15 or Seq. ID. No. 16 under stringent hybridization conditions.

6. An isolated nucleic acid that codes for a full length DPD polypeptide, wherein a polypeptide expressed from the nucleic acid specifically binds to an antibody generated against an immunogen consisting of a DPD polypeptide having an amino acid sequence as depicted by Seq. ID. No. 2 or Seq. ID. No. 4."

Claims 2 to 5 related to specific embodiments of claim 1 and claims 7 to 10 concerned specific embodiments of claim 6. In claims 3 and 8, the isolated nucleic acid consisted of the human polynucleotide sequence of Seq. ID. No. 15 and in claims 5 and 10, the isolated nucleic acid consisted of the pig polynucleotide sequence of Seq. ID. No. 16.

Claim 11 was directed to an oligonucleotide probe. Claims 13 to 20 concerned specific embodiments of independent claim 12, which was directed to an *in vitro* method for determining whether a patient was at risk of a toxic reaction to 5-fluorouracil, the method comprising analyzing DPD DNA or mRNA in a sample from the patient to determine if the patient was deficient in DPD nucleic acids. Claims 21 to 23 were directed to a method for expressing the nucleic acid of claim 1 in

a prokaryotic cell. And, claims 24 to 28 related to an expression vector comprising a selectable marker, wherein the selectable marker was a nucleic acid of claim 1 operably linked to a promoter.

XI. The **auxiliary request** read as the main request except for the deletion of claims 6 to 10 of the main request.

XII. The appellant's arguments, insofar as relevant to the present decision, may be summarized as follows:

Main request and auxiliary request
Articles 123(2) and 84 EPC

The claims were directed to Seq. ID. Nos. 15 and 16 filed with the grounds of appeal and corresponding, respectively, to the cDNA sequences of Figure 1A-1B and Figure 2 of the priority document US 08/304 309. These sequences were considered to be the true sequences.

There was a disparity between the nucleotide sequence of Seq. ID. No. 15 - encoding a glycine (Gly) at position 787 of the human DPD protein - and this of Figure 1A-1B of the application as filed - encoding an arginine (Arg) at position 787 of the human DPD protein. However, the skilled person recognized the discrepancy and resolved it by noting that the nucleotide sequences of Seq. ID. No. 2 (human) and of Figure 3 (human and pig) showed a Gly at position 787 and thus, clarifying that the codon shown in the amended "Sequence Listing" (Seq. ID. No. 15) was the correct one. The skilled person concluded thereby that the single nucleotide difference in the codon (**G**GA vs. **C**GA) was a typographical error in the sequence of Figure 1.

Although the nucleotide sequence of Seq. ID. No. 16 differed from that of Figure 2 of the application as filed (due to the presence of the nucleotides C and G at positions 3342 and 3358, respectively, instead of G and C), these nucleotides were located well into the 3' untranslated region. Therefore, the skilled person considered this discrepancy at best to be unimportant because probes were usually designed to bind to the coding region and not to portions of the untranslated regions just outside the coding region, if only to avoid the hybridization to genes sharing similar regulatory elements to those of the gene of interest but which were unrelated thereto. The errors at positions 3342 and 3358 did not effect the ability of the invention to solve the technical problem.

In case that the nucleotide sequence of Seq. ID. No. 16 was considered to be unacceptable by the board, the appellant indicated its willingness to revert to the nucleotides present at positions 3342 and 3358 of Figure 2 of the application as filed. Since the errors at positions 3342 and 3358 of Figure 2 did not effect the ability of the invention to solve the objective technical problem, the presence of these errors did not affect the priority claim of the invention, regardless of whether corrections were made or not. In the event that the replacement of the nucleic acid sequence of Seq. ID. No. 16 by this of Figure 2 of the application as filed was considered to invalidate the priority claim of the application, the appellant expressed its agreement to restrict the claimed subject-matter to the human DPD related sequences only.

Since all discrepancies were with respect to the 3' untranslated region, the claims were unaffected as they were directed to isolated nucleic acids encoding DPD and hybridizing to the sequences of Seq. ID. Nos. 15 or 16. Since the claimed nucleic acids had a coding region of over 3000 nucleotides (the DPD protein had over 1000 amino acid residues), a difference of a few nucleotides in the 3' untranslated region did not affect the hybridization of the claimed nucleic acids.

XIII. The appellant (applicant) requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of either the main request or the auxiliary request, both filed on 12 May 2008.

Reasons for the Decision

Main request and auxiliary request
Article 123(2) EPC

The claimed subject-matter

1. Claim 1 of both the main and the auxiliary requests is directed to an isolated nucleic acid encoding a dihydropyrimidine dehydrogenase (DPD) protein which is characterized by being capable of selectively hybridizing to a second nucleic acid consisting of the nucleotide sequence of Seq. ID. Nos. 15 or 16 under stringent hybridization conditions. Claims 3 and 5 of these requests further characterize this isolated nucleic acid as consisting, respectively, of the human nucleotide sequence of Seq. ID. No. 15 or of the pig nucleotide sequence of Seq. ID. No. 16. Claim 6 of the

main request is directed to an isolated nucleic acid that codes for a full length DPD polypeptide, wherein claims 8 and 10 further characterize this isolated nucleic acid as consisting, respectively, of the human nucleotide sequence of Seq. ID. No. 15 or of the pig nucleotide sequence of Seq. ID. No. 16 (cf. Sections X and XI *supra*).

2. Thus, on the one hand, the claimed subject-matter embraces a group of nucleic acid sequences capable of hybridizing to the specific nucleic acid sequences of Seq. ID. Nos. 15 and 16 and, on the other hand, it comprises, as particular embodiments, the very specific nucleic acid sequences of Seq. ID. Nos. 15 and 16.

The specific nucleic acid sequences of both the main and the auxiliary requests

3. The nucleic acid sequences of Seq. ID. Nos. 15 and 16 are among seventeen sequences present in an amended "Sequence Listing" filed as Annex 2 with the appellant's grounds of appeal (cf. Section III *supra*). This amended "Sequence Listing" is different from the "Sequence Listing" of the application as filed which consists of thirteen sequences only (Seq. ID. No. 1 to Seq. ID. No. 13) (cf. pages 43 to 62 of the application as filed).

4. In particular, Seq. ID No. 15 corresponds to a nucleic acid sequence encoding a human DPD protein and thus, should be identical to the nucleic acid sequence of Figure 1 of the application as filed and to the nucleic acid sequence of Seq. ID. No. 1 of the "Sequence Listing" of the application as filed, both sequences

being defined in the application as filed as the nucleotide sequence of a human DPD protein (cf. page 4, lines 13 to 14 and page 43, line 60 of the application as filed).

5. It is noted, however, that the specific nucleic acid sequence of Seq. ID. No. 15 differs at position 2440 from this of Figure 1 of the application as filed. At this position, Seq. ID. No. 15 has the nucleotide (G), whereas Figure 1 has the nucleotide (C). This difference results in a different codon (**G**GA vs. **C**GA) which translates in a different amino acid residue (glycine vs. arginine) at position 787 of the human DPD amino acid sequence. Moreover, the nucleic acid sequence of Seq. ID. No. 15 differs also from this of Seq. ID. No. 1 of the "Sequence Listing" present in the application as filed. Although both sequences have identical nucleotides (G) and codons (**G**CA) translating to identical amino acid residues (glycine) at position 787 of the amino acid sequence of the human DPD, Seq. ID. No. 15 does not have the first six nucleotides (AGACAC) of Seq. ID. No. 1, has a different nucleotide (C) at position 3813 (which corresponds to nucleotide (G) at position 3816 of Seq. ID. No. 1) and has three undefined nucleotides (N) at positions 3350, 3671 and 3720 which are not present in Seq. ID. No. 1.

6. With regard to Seq. ID. No. 16, which corresponds to a nucleic acid sequence encoding a pig DPD protein, it should be identical to the nucleic acid sequence of Figure 2 of the application as filed and to the nucleic acid sequence of Seq. ID. No. 3 of the "Sequence Listing" of the application as filed, both sequences being defined in the application as filed as the

nucleotide sequence of a pig DPD protein (cf. page 4, line 15 and page 52, line 19 of the application as filed).

7. It is noted, however, that the specific nucleic acid of Seq. ID. No. 16 differs at positions 3342 and 3358 from this of Figure 2 of the application as filed. At these positions, Seq. ID. No. 16 has the nucleotides (C) and (G) instead of the nucleotides (G) and (C) present in Figure 2. Moreover, the nucleic acid sequence of Seq. ID. No. 16 differs also from this of Seq. ID. No. 3 of the "Sequence Listing" of the application as filed. Although both sequences have identical nucleotides (C) and (G) at corresponding positions (3348 and 3364 in Seq. ID. No. 3), the nucleic acid sequence of Seq. ID. No. 16 does not have the first six nucleotides (GGACAC) of Seq. ID. No. 3.

8. It follows from the above that the nucleic acid sequences of Seq. ID. Nos. 15 and 16 of the "Sequence Listing" of "Annex 2" filed with the appellant's grounds of appeal are, respectively, a combination of the specific nucleic acid sequences of Figure 1 and Seq. ID. No. 1 and of Figure 2 and Seq. ID. No. 3 of the application as filed, but both nucleic acid sequences are different from those present in the application as filed, i.e. they are added subject-matter within the meaning of Article 123(2) EPC.

9. In reply to the board's communication (cf. Section VI *supra*), the appellant acknowledged the presence of these differences and attributed them to the use of alternative filters. The appellant further stated that the nucleic acid sequences of Seq. ID. Nos. 15 and 16

correspond, respectively, to the nucleic acid sequences of Figures 1 and 2 of the priority document (US 08/304 309) and that they "*are considered by the Applicant to be the true sequences*". It is, however, established case law of the Boards of Appeal that the content of the application as filed does not include the priority document (cf. "Case Law of the Boards of Appeal of the EPO", 5th edition 2006, III.A.1.1, page 235). A feature disclosed in the priority document but not directly and unambiguously derivable from the application as filed represents an inadmissible extension within the meaning of Article 123(2) EPC.

Conclusion

10. In conclusion, both the main and the auxiliary requests, in so far as they are directed to the specific nucleic acid sequences of Seq. ID. Nos. 15 and 16, do not fulfil the requirements of Article 123(2) EPC.

Further issues and considerations of the board

11. Although, in reply to the board's communication, the appellant indicated its willingness to revert the claimed subject-matter to the specific nucleic acid sequences of the application as filed and/or to restrict the claimed subject-matter to human DPD related sequences only (cf. Section XII *supra*), no formal request has been put forward before the board other than the main request and the auxiliary request filed both on 12 May 2008. The board, therefore, sees no reason to examine in detail the issues that other possible requests would raise, in particular, the clarity of the nucleic acid sequences present in the

application as filed, the correction of possible errors within these sequences and the right or entitlement of these sequences to the claimed priority.

12. Nevertheless, it derives from the above discussion on the nucleic acid sequences of Seq. ID. Nos. 15 and 16 that several differences are present between the nucleic acid sequence of Figure 1 and this of Seq. ID. No. 1 of the application as filed (both encoding a human DPD protein) as well as between the nucleic acid sequence of Figure 2 and this of Seq. ID. No. 3 of the application as filed (both encoding a pig DPD protein) (cf. points 3 to 9 *supra*). In view of the nature of these differences and their position within the corresponding nucleic acid sequences, it is arguable whether a correction for each and every one of these differences - both within the coding region as well as within the 5' and/or 3' non-coding regions - is immediately evident to the skilled person and directly derivable from the application as filed, being these the conditions defined in the case law for allowing a correction of the application as filed (cf. "Case Law", *supra*, III.D, page 277).

13. Moreover, the fact that none of the nucleic acid sequences of the application as filed is identical to the nucleic acid sequences of Figures 1 and 2 of the priority document, which in the words of the appellant "*are considered to be the true sequences*", makes the allowability of such corrections even more doubtful. In so far as other possible - but not formally filed - requests suggested by the appellant contemplate the presence of claims directed to those very specific nucleic acid sequences *per se*, the appellant's

arguments, based mainly on the small number of differences, their location outside the coding region and the ability of all sequences to solve the objective problem of the invention (cf. Section XII *supra*), are not relevant.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

A. Wolinski L. Galligani