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D E C I S I O N
of 11 November 2002

Case Number: T 0950/99 - 3.3.8

Application Number: 87303944.0

Publication Number: 0244267

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Variants of decay accelerating factor (DAF) prepared by recombinant DNA technology

Patentee:
GENENTECH, INC., et al.

Opponent:
Imutran Limited

Headword:
Decay accelerating factor/GENENTECH

Relevant legal provisions:
EPC Art. 56, 108

Keyword:
"Admissibility of appeal (yes)"
"Admissibility of additional documents filed with the statement of grounds of appeal (yes)"
"Inventive step (yes)"

Decisions cited:
J 0022/86, T 0455/91, T 0386/94, T 1208/97, G 0010/91

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0950/99 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 11 November 2002

Appellant: (Opponent)
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Representative:
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 30 July 1999 concerning maintenance of European patent No. 0 244 267 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
S. U. Hoffmann

Summary of Facts and Submissions

I. The opponents (the appellants) lodged an appeal against the interlocutory decision of the opposition division dated 30 July 1999, whereby the European patent No. 0 244 267, which they had opposed under Article 100(a) EPC (on grounds of lack of novelty and lack of inventive step) and Article 100(b) EPC, was maintained on the basis of the first auxiliary request with 54 claims filed on 4 May 1999.

II. Claim 1 of the first auxiliary request read as follows:

"1. Nucleic acid which encodes mDAF as shown in Figure 1, sDAF as shown in Figure 2, or an amino acid sequence variant thereof wherein a predetermined amino acid residue or polypeptide is inserted into, deleted from or substituted for an amino acid residue or polypeptide of the native mature or preDAF amino acid sequence of mDAF shown in Figure 1 or sDAF shown in Figure 2, the variant being capable of exhibiting a biological activity in common with said mDAF or sDAF; which nucleic acid is (a) DNA free of an intron or (b) DNA free of flanking genomic DNA or (c) cell-free or (d) free of nucleic acid encoding any other protein homologous to the source of the nucleic acid which encodes DAF."

Independent claim 29 was directed to sDAF.

Independent claim 30 was directed to nucleic acids capable of hybridizing with nucleic acid encoding mDAF, sDAF or a variant thereof.

Independent claim 31 was directed to nucleic acid

encoding a particular variant of mDAF.

Independent claim 32 was directed to a replicable vector containing a nucleic acid encoding mDAF, sDAF or a variant thereof.

Independent claim 34 was directed to a composition comprising a host cell transformed with said vector.

Independent claim 36 was directed to a method of making mDAF, sDAF or a variant thereof comprising culturing a host cell transformed with such a vector.

Independent claim 40 was directed to mDAF or sDAF unaccompanied by native glycosylation.

Independent claim 43 was directed to a pharmaceutical composition comprising an immunomodulatory conjugate of mDAF or sDAF.

Independent claim 48 was directed to a composition comprising an antibody capable of binding sDAF.

Independent claim 50 was directed to a polypeptide comprising a phospholipid anchor domain of mDAF fused to a polypeptide other than DAF.

Independent claim 51 was directed to a polypeptide which was a fusion of the C-terminal domain of mDAF and a polypeptide other than DAF.

III. Together with their statement setting out the grounds of appeal, the appellants filed five additional documents (cf documents (D58) to (D62) in section VII infra).

In said statement, three grounds of appeal were referred to. However, whereas lack of inventive step was discussed in detail, with respect to both lack of novelty and insufficiency of disclosure it was only stated that the appellants had no further remarks at this stage.

IV. The respondents (the patent proprietors) replied to the statement of grounds with a letter dated 21 August 2000. They objected *inter alia* to the introduction of the new documents into the proceedings.

V. On 5 August 2002, the board issued a communication with a provisional view on some of the issues to be discussed at oral proceedings.

VI. Oral proceedings took place on 11 November 2002. They were only attended by the respondents, the appellants having announced in a letter dated 25 September 2002 that they would not attend.

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

(D2) Nicholson-Weller A. et al., J. Immunol., Vol. 129, No. 1, July 1982, Pages 184 to 189

(D3) Medof M. E. et al., J. Exp. Med., Vol. 160, No. 5, November 1984, Pages 1558 to 1578

(D6) Medof M. E. et al., Proc. Natl. Acad. Sci. USA, Vol. 84, No. 7, April 1987, Pages 2007 to 2011

(D10) Nicholson-Weller A. et al., Proc. Natl. Acad. Sci. USA, Vol. 80, August 1983, Pages 5066

to 5070

(D16) Kinoshita T. et al., J. Exp. Med., Vol. 162, July 1985, Pages 75 to 92

(D30) Medof M. E. et al., Complement, Vol. 2, November 1985, Abstract 151, Pages 53 to 54

(D51) Nicholson-Weller A. et al., Blood, Vol. 66, No. 5, 1985, Pages 1237 to 1244

(D58) Pangburn M. K., J. Immunol., Vol. 136, No. 6, 15 March 1986, Pages 2216 to 2221

(D59) Declaration of Dr R. A. Harrison dated 9 December 1999

(D60) Tomita M. et al., Proc. Natl. Acad. Sci. USA, Vol. 72, No. 8, August 1975, Pages 2964 to 2968

(D61) Declaration of Dr M. K. Pangburn dated 8 December 1999

(D62) Pangburn M. K. et al., Proc. Natl. Acad. Sci. USA, Vol. 80, September 1983, Pages 5430 to 5434

(P4) Davitz M. A. et al., J. Immun. Meth., Vol. 97, 1987, Pages 71 to 76

(P8) Sugita Y. et al., J. Biochem., Vol. 100, No. 1, July 1986, Pages 143 to 150

(P9) Declaration of Dr V. Nussenzweig dated 3 March 1998

(A) First declaration of Dr D. M. Lublin dated 18 October 1996

(B) Declaration of Dr A. Nicholson-Weller dated 29 October 1996

(C) Declaration of Prof M. L. Tykocinski dated 3 March 1999

VIII. The arguments in writing by the appellants, insofar as they are relevant for the decision, can be summarized as follows:

Filing of documents (D58) to (D62)

The appellants became aware of document (D58) only days ahead of the oral proceedings held before the opposition division on 4 May 1999. A request was made at said oral proceedings to have the document admitted into the proceedings, but it was not admitted; and the minutes unfortunately did not identify the document when recording the request in section 7.7. thereof.

No reasons were indicated as to the filing of documents (D59) to (D62) only at the appeal stage.

Article 83 EPC: sufficiency of disclosure

The appellants only stated that they had "nothing to add at this stage to the comments made at first instance".

Article 54 EPC: novelty

The appellants only stated that they had "no further remarks on the question of novelty at this stage".

Article 56 EPC: inventive step

The technical problem to be solved on the basis of the closest prior art, in accordance with a statement in the patent (see page 3, lines 50 to 51), was the preparation of DAF in commercial quantity from a therapeutically acceptable source, the solution to said problem being the provision of nucleic acid encoding DAF and the related subject-matter, as set out in the claims.

Two parallel lines of reasoning were given, differing only in that either document (D3) or document (D58) was chosen as the closest prior art.

Choosing document (D3) as the closest prior art, they argued as follows. Document (D3) disclosed DAF purified to homogeneity sufficiently for it to be sequenced. The particular relevance of document (D3) originated from the admission by the authors that they actually had purified DAF to homogeneity. No evidence was provided that glycophorin contamination as referred to in the declaration of Dr V. Nussenzweig (document (P9)) was anything other than an individual batch-specific problem. Nothing indicated that this was a general problem with the methodology of document (D3). Nevertheless, even if glycophorin was repeatedly present in DAF prepared by said methodology, it would not have caused major difficulties. As the N-terminal amino acid sequence of glycophorin was known at the priority date from document (D60), it would have been a straightforward matter to sequence the N-terminus of the "wanted" DAF.

Choosing document (D58) as the closest prior art, they

similarly argued that said document disclosed a method for obtaining DAF purified to homogeneity, the authors of the document having stated that "[A]ll the purified proteins [which included DAF] were homogeneous ...". Being homogeneous, said DAF was sequenceable.

They contended that if unsequenceable DAF was obtained by employing either the methodology of document (D3) or that of document (D58) this could anyway be purified to such an extent to make it sequenceable by immunopurifying the DAF preparation using the anti-DAF monoclonal antibody IA10. Said antibody had been made available to the public at the priority date. In this respect reference was made to document (D16). It was also noted that at the priority date said antibody was in possession of Dr M. E. Medof who could be considered a member of the public. It was also common knowledge at same date that varying the pH to determine optimal elution conditions for the immunopurification was a routine measure for those skilled in the art. There were good reasons for using high pH and said conditions were not exceptional.

The appellants also expressed the view that, insofar as sequenceable DAF was available, cloning DAF DNA as such did not involve an inventive step. There was a reasonable expectation that this could be achieved successfully. In this respect, reference was made to decision T 386/94 (OJ EPO 1996, 658).

IX. The arguments in writing and during oral proceedings by the respondents, insofar as they are relevant to the present decision, can be summarized as follows:

Procedural issues:

Documents (D58) to (D62) should not be admitted into the appeal proceedings as being late-filed. If it was decided to admit them, the case had to be referred back to the opposition division and the appellants had to bear the costs thereof. This was because an attack on inventive step based on these documents represented a change in the legal and factual framework and was therefore a fresh ground of opposition which could not be admitted on appeal without the patent proprietors' consent (cf G 10/91, OJ EPO 1993, 420). They observed also that in any case document (D58) was not more relevant than document (D3) already on file.

Lack of novelty and insufficiency of disclosure should not be regarded as valid grounds of appeal, for the reason that they were not substantiated.

Article 56 EPC: inventive step

The respondents argued that both the provision of purified, sequenceable DAF allowing for a cloning attempt and the cloning of full-length DAF-encoding DNA involved an inventive activity.

The DAF preparation of document (D3) was highly contaminated with glycophorin and unsequenceable, despite having already been treated with anti-glycophorin antibodies. The contamination of the preparation of document (D3) would not have been apparent to the ordinary person skilled in the art who would only have had the teaching of document (D3) on which to go. Unaware of its impurity, the skilled person would have failed to obtain DAF sequence from the preparation of document (D3).

No one succeeded in obtaining a DAF sequence from the preparation of document (D58). In said document the homogeneity of DAF as such was not documented.

Indeed, in succeeding, both the "Genentech/New York University" team (below referred to as "the Genentech/NYU team"; respondents' search team) and the "Case Western Reserve University/Washington University" (below referred to as "the CWRU/WU team", a competitor search team) made use of the antibody IA10 which was not available to the public. Both teams used said antibody in immunopurification and found that unusual and non-obvious elution conditions were required for success. The prior art did not indicate a reasonable expectation that success would be achieved using immunopurification. Still further, even after obtaining purified, sequenceable DAF, the cloning efforts of both teams involved inventive activity even once sequenceable DAF had been obtained as the choice of neither the probes nor the cDNA libraries was obvious.

X. The appellants requested that the decision under appeal be set aside and the patent be revoked.

XI. The respondents requested that the appeal be dismissed, and, auxiliary, in the case where documents (D58) to (D62) would be admitted into the proceedings, that the case be remitted to the first instance and the costs be apportioned in their favour.

Reasons for the Decision

Admissibility of the appeal

1. The statement setting out the grounds of appeal includes the legal and factual reasons why the decision under appeal should be set aside with respect to at least one ground, namely lack of inventive step. Therefore, even if it does not contain a full reasoning with respect to each and every ground, nevertheless said statement meets the minimum requirement of Article 108 EPC (see decision J 22/86, OJ EPO 1987, 280, point 2 of the reasons).

2. As also the requirements of Article 107 EPC and Rule 64 EPC are met, the appeal is admissible.

Admissibility into the appeal proceedings of documents (D58) to (D62)

3. Five additional documents ((D58) to (D62)) were filed together with the statement of grounds. The respondents are vehemently against their admission into the proceedings as, in their view, an attack based thereupon creates a new case. On the other hand, they submit that document (D58) is no better than document (D3) already on file.

4. Although, in principle, an appeal should be essentially based on facts and evidence which were already available to the department of the first instance, parties in their effort to make a full statement of the grounds why the revision of the contested decision is requested often rely on additional evidence. Such evidence, especially when filed at the onset of the appeal, is not necessarily defined as being "late-filed". Much depends on its *prima facie* relevance, the board being empowered essentially either (i) to disregard it under Article 114(2) EPC or (ii), having

admitted it, to remit the case to the department of first instance under Article 111(1) EPC for further prosecution, or (iii), having admitted it, to decide on the case.

5. In the present case, the board, exercising its discretion, decides to admit documents (D58) to (D62) into the appeal proceedings, and to adopt the option (iii) for the following reasons: (a) the said documents have been filed at the onset of the appeal essentially for providing an additional support to the appeal; (b) the said documents do not add any further elements which could convince the board to adopt a different position as regards inventive step when compared to the ones already on file.

The grounds of appeal other than lack of inventive step

6. The respondents have requested that the alleged lack of novelty and insufficiency of disclosure be disregarded by the board as not having been substantiated in the statement of grounds.

7. A mere reference to arguments made during proceedings before the department of the first instance is *per se* not sufficient for a valid statement of grounds. However, as stated above (cf point 1), in the present case the statement of grounds contains the appellants' complete case on the issue of inventive step. As regards the remaining issues of novelty and sufficiency of disclosure, the board, in view of the fact that the appellants failed to provide a full statement of the grounds why the contested decision is wrong, sees no reasons to deviate from the decision of the opposition division.

Inventive step

8. The appellants have regarded documents (D3) and (D58) as being appropriate to represent the closest prior art.

9. Document (D3) describes in a short passage (cf chapter "Purification and characterization of DAF" on page 1560) *inter alia* a method for the purification of the decay-accelerating factor (DAF). The description is brief. The method is said to be derived from the Nicholson-Weller et al. method as described in document (D10), the **modified** fractionation sequence described by said authors being used in the initial phases of the isolation. Said phases are not detailed. They were followed by a treatment with Sepharose beads coupled to monoclonal antibodies to remove contaminating C3b/C4b receptor (CR1) and glycophorin A, the monoclonal antibodies to glycophorin used being merely defined as a "gift" of a scientist (cf chapter "Reagents, and Proteins" on page 1559). The resulting fraction was then subjected to additional chromatography on DEAE-Sephacel, followed by molecular sieving at high pressure liquid chromatography (HPLC). Said chromatographies are not detailed but it is indicated that **details in their respect will be described elsewhere**. The recovered DAF preparation was analysed by SDS-PAGE and silver staining, Western blotting, and by radiolabeling followed by HPLC. On the basis of said analysis, the authors concluded that they had **purified DAF to homogeneity** as evidenced by the presence of a single band on radioautographs of SDS-PAGE gels.

10. Document (D58) also provides a brief description of a method for the purification of DAF (cf top of the left-hand column of page 2217). Said method was derived from the Nicholson-Weller et al. method as described in document (D2). The modifications to said method for which **reference to a manuscript in preparation** is made are only briefly described. A sentence which applies not only to DAF but also to the complement components used in the study, with which document (D58) principally deals, indicates that the purified proteins were **homogeneous** on polyacrylamide gel electrophoresis in the presence of SDS as assessed by Coomassie dye or silver stain.

11. As evidenced above, documents (D3) and (D58) are essentially equivalent in their disclosure with respect to the method for purifying DAF they each describe. Both claim to have achieved purification based on homogeneous bands observed upon electrophoresis on polyacrylamide gels. Neither of them discloses any amino acid sequence data.

12. In the board's judgment, document (D58) is no better than document (D3). Since this latter was cited in the notice of opposition and was considered by the appellants to represent the closest prior art at the oral proceedings before the opposition division, the board takes it as the closest prior art.

13. The technical problem to be solved is regarded as the provision of human DAF and variants thereof in purified form in high amounts for the purpose of preparing pharmaceutical compositions. The solution proposed is a method and means for producing it by genetic engineering.

14. The question to be answered is whether it would have been obvious for the person skilled in the art to try to produce DAF by genetic engineering with a reasonable expectation of success.

15. At the priority date (in May 1986) it was known that DAF was present on the membrane of red cells and other blood elements in contact with the complement system, ie platelets, neutrophils, monocytes, B and T lymphocytes (cf document (D16), page 76 and document (D51), right-hand column of page 1237). Document (D30) contained the preliminary (as being in the form of an abstract) additional information that membrane-associated DAF antigen had been identified also outside the vascular space and that soluble DAF had been detected.

16. The person skilled in the art, a person with a practical, pragmatic approach (cf T 1208/97 of 3 November 2000) and with a caution attitude (cf T 455/91, OJ EPO 1995, 684), based on the prior art, would have considered that, although erythrocytes were an appropriate source of DAF, this protein, being a membrane protein, could be extracted therefrom only in too small quantities for envisaging its use in the preparation of pharmaceutical compositions at a larger scale, and that extraction of DAF from erythrocyte stromas might be associated with the risk of the DAF preparation being contaminated with CR1 and/or glycophorin.

17. The person skilled in the art was also aware of the fact that for human proteins which one could not easily obtain in purified form from a natural source a possible alternative for obtaining higher quantities in

a form devoid of other contaminants was using the genetic engineering route.

18. Thus, the person skilled in the art would have envisaged preparing DAF using the genetic engineering route, well aware, however, of the fact that, although devising on paper a theoretical experimental plan was feasible, the actual achievement of a result might not be a matter of routine, much depending upon the relevant information already available in the art.

19. Preparing DAF by genetic engineering techniques required first of all the cloning of a DNA encoding DAF. This required the availability of amino acid sequence data reliable enough to allow the design of oligonucleotide probes for screening eg a cDNA library made from a cell/tissue source that contained DAF mRNA.

20. As regards the amino acid sequence data, no information whatsoever was available from any of the prior art documents cited by the parties. This is confirmed *inter alia* by the first declaration of Dr D. M. Lublin (document A) who stated that "[He] was not aware of any sequence information on DAF when [he] began [his] project" (cf point 8 of the declaration). Thus, an important piece of information was missing in the art. The skilled person knew that success in the project much depended on the ability of acquiring such reliable sequence data and that for this highly purified, homogeneous DAF was needed.

21. Document (D3) reported that DAF purified to homogeneity had been obtained. This was indeed a suitable starting point for the skilled person who however would have immediately realised, firstly, that the full details of

the modified method described in (D3) were going to be described elsewhere; secondly, that the alleged homogeneity was essentially based on the observation of a single band on radioautographs of SDS-PAGE gels; and thirdly, that the repetition of the experimental protocols of (D3) presupposed the availability of suitable monoclonal antibodies. Thus, when embarking in the repetition of the work described in (D3), the skilled person was already faced with a number of uncertainties.

22. The unavailability of a detailed protocol would have forced the skilled person to look for further references of the same group of scientists in the effort to complete the information.

23. Furthermore, the skilled person knew that the observation of a single band on SDS-PAGE gels was not necessarily indicative of a purity sufficient for rendering a protein "sequenceable". As a matter of fact, the whole of the evidence on file in the present case shows that removal of glycophorin was one of the major factors impeding the purification of DAF (cf eg the declaration of Dr V. Nussenzweig (document (P9)) and the later document (P8)).

The appellants' position in this respect is essentially that the skilled person's expectation would have been that the D3 material would have yielded DAF protein sequence data (cf Dr R. A. Harrison's declaration, document (D59)) or that, even if some glycophorin existed, this could have been removed by standard techniques (cf declaration of Dr A. Nicholson-Weller, document (B)) or that, even in the presence of glycophorin contamination, the DAF sequence could still

have been deduced as the glycophorin sequence was known (cf Dr R. A. Harrison's declaration, document (D59)).

However, in the board's judgement, the absolute lack of any amino acid sequence information in the prior art was a decisive element of uncertainty for the skilled person, all the statements about the likelihood to obtain useful sequence information based on the D3 material being a matter of subjective interpretation. As a matter of fact, the real breakthrough in DAF purification and cloning by both the Genentech/NYU team and the CWRU/WU team was made possible by the use of immunoaffinity chromatography with the specific monoclonal antibody IA10 (cf documents (D6), (P4) and (A)).

24. The appellants submitted that the person skilled in the art would have regarded it as a normal approach to prepare a sequenceable DAF preparation using an immunochromatography involving the antibody IA10 which was described in document (D16) or a related antibody.

25. As regards this argument, it is noted that document (D3) indicated to the skilled person the route of using monoclonal antibodies against the contaminants CR1 and glycophorin, not against DAF *per se*. Such antibodies were not immediately available either commercially or via a wide scientific network, and thus had to be prepared. At any rate, the skilled person knew that the preparation of suitable monoclonal antibodies to be used in an immunopurification process was *per se* not a simple matter of routine.

As for the possibility of using the particular monoclonal antibody IA10, it is observed that, although

this was described, together with two other monoclonal antibodies, in document (D16), this was in the context of studying DAF distribution in the peripheral blood of normal individuals and patients with paroxysmal nocturnal hemoglobinuria, not in the context of DAF purification. Neither document (D16) nor any other prior art document provided the skilled person with a hint about the possible usefulness of the specific monoclonal antibody IA10 in an immunopurification of DAF, not to mention the particular elution conditions to be used. Moreover, apart from all the difficulties linked to the reproduction of the said antibody on the basis of the description provided by document (D16), there is also the question of the public availability of such an antibody, which - as shown also by WO-86/07 062 (a document cited during the examination procedure) - was proprietary, having been developed at the New York University by a team which included also Drs V. Nussenzweig and M. E. Medof, named inventors in the cited international patent application. The appellants submitted that when leaving the Genentech/NYU team Dr M. E. Medof took with him the antibody and, as a consequence, the antibody was made available to at least one member of the public, ie Dr M. E. Medof. However, this argument cannot be followed by the board: Dr M. E. Medof, who became member of a competitor team at CWRU/WU, cannot be considered as a member of the public who could freely distribute the said monoclonal antibody. This is confirmed also by the declaration of Prof M. L. Tykocinski (document (C)), a member of the CWRU/WU team, who stated "It was important that **material** and information be kept **confidential** between the two groups at CWRU and WU, as [they] hoped to be the first to clone DAF and publish those results before

others" (emphasis added by the board).

26. Thus, in the board's judgment, the skilled person would not have derived from the prior art relative to allegedly homogenous preparations of DAF any particular expectations to obtain useful amino acid sequence data which would have lead in a straightforward manner to the design of oligonucleotide probes that would have made easy the cloning of a DNA sequence encoding DAF. Under the technical circumstances of the present case, the skilled person would have rather expected the task not to be an easy one and to depend also upon the ability of devising and performing appropriate modifications in existing theoretical protocols or even of taking a different approach.

27. The comparison made by the appellants with the case of T 386/94 (supra) is not appropriate as the technical circumstances of that case were completely different because the prior art had already disclosed relevant data for the cloning such as *inter alia* the prochymosin mRNA and a DNA molecule encoding 80% of prochymosin.

28. In conclusion, the board considers that, having regard to the state of the art, the subject-matter of the claims at issue, ie those maintained by the opposition division (cf section I above), was not obvious to the person skilled in the art.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani