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D E C I S I O N
of 24 February 2004

Case Number: T 1201/02 - 3.3.8

Application Number: 98943469.1

Publication Number: 0998569

IPC: C12N 15/56

Language of the proceedings: EN

Title of invention:
Polynucleotide encoding a polypeptide having heparanase activity and expression of same in transduced cells

Applicant:
Insight Strategy & Marketing Ltd., et al.

Opponent:
-

Headword:
Heparanase/INSIGHT STRATEGY

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Novelty - yes"
"Inventive step - yes"

Decisions cited:
-

Catchword:
-

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Case Number: T 1201/02 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 24 February 2004

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 31 May 2002 refusing European application No. 98943469.1 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
M. B. Günzel

Summary of Facts and Submissions

I. European patent application No. 98 943 469.1 published under the International Publication No. WO 99/11798 with the title: "Polynucleotide encoding a polypeptide having heparanase activity and expression of same in transduced cells." was refused by the Examining Division.

The reasons for the refusal were lack of novelty of claims 19 to 27 and lack of inventive step of claims 1 to 18 and 28 to 35 of the request then on file.

II. The Appellants (Applicants) appealed this decision and submitted a statement of grounds of appeal together with a new main request and an auxiliary request.

III. The Board sent a communication under Article 11(1) of the Rules of Procedure of the Boards of appeal indicating its preliminary, non-binding opinion as to the formal admissibility, clarity and novelty of the newly filed claims.

IV. In answer to this communication, the Appellants filed new submissions together with a new main request and a new auxiliary request.

V. At oral proceedings which took place on 24 February 2004, these requests were replaced by a request comprising 15 claims. Claims 1, 6, 10, 11 and 13 read as follows:

"1. An isolated polynucleotide fragment comprising a polynucleotide sequence encoding a polypeptide having heparanase catalytic activity, wherein said polypeptide shares at least 70% homology with SEQ ID NOs: 10 or 14 or a functional fragment thereof having heparanase catalytic activity."

"6. A polynucleotide fragment comprising a polynucleotide sequence at least 70% homologous with SEQ ID NOs: 9 or 13, said polynucleotide sequence encoding a polypeptide having heparanase catalytic activity."

"10. A recombinant protein which is a polypeptide of 543 amino acids as set forth in SEQ ID NO: 10 with a calculated molecular weight of 61,192 daltons or a functional part thereof."

"11. A polypeptide of 592 amino acids as set forth in SEQ ID NO: 14 with a calculated molecular weight of 66,407 daltons or a functional part thereof."

"13. A medical device containing, as an active ingredient, an isolated protein/polypeptide according to claim 10 or 11."

Dependent claims 2 to 5 related to further features of the polynucleotide of claim 1, dependent claim 7 related to further features of the polynucleotide of claims 1 to 6. Dependent claims 8 and 9 related to a vector and a host cell comprising the polynucleotide of any of claims 1 to 7. Dependent claim 12 related to a pharmaceutical composition comprising the protein/polypeptide according to claim 10 or 11.

Claims 14 and 15 containing back references to claims 1 to 7 and to claims 6 or 7 respectively related to a system for over-expressing heparanase and to a method of identifying a chromosome region harbouring a heparanase gene.

VI. The following documents are mentioned in the present decision:

(1): Jin, L. et al., Proceedings of the American Association for Cancer Research, Annual meeting 1992, Abstract 343, Vol.33, page 57, 1992,

(3): US 5,362,641;

(4): WO 95/04158;

(9): Declaration of Dr I. Vlodavsky dated 12 June 2003, submitted on 23 January 2004;

(10): Declaration of Dr I. Pecker dated 9 June 2003, submitted on 23 January 2004.

VII. The Appellants' arguments may be summarized as follows:

Novelty

The prior art disclosed neither the isolation of the heparanase encoding DNA, nor the existence of prepro- or pro- forms of the enzyme. Accordingly, the subject-matter of independent claims 1 and 6 (DNA claims) and 10 and 11 (protein/polypeptide claims) as well as that of the other claims which were either dependent thereon or contained a back-reference thereto was novel.

Inventive step

The closest prior art document was document (3) which described the purification of heparanase from human cells.

In view of the closest prior art, the technical problem underlying the present invention was to provide a nucleic acid molecule encoding mammalian heparanase. The solution to this problem was the DNA molecule as defined in claim 1.

It was only with hindsight that the skilled person would derive the above mentioned problem from document (3) since this document disclosed a complete heparanase purification scheme and did not suggest that some other path should be chosen when wanting to obtain the enzyme in pure form.

The skilled person had no reasonable expectation of success of cloning the heparanase gene for at least the following reasons:

– the heparanase purification protocol described in document (3) did not yield a pure enzyme preparation. When attempting to obtain a partial amino acid sequence of heparanase, a number of peptides would be identified which in fact, did not belong to the protein. This, of course, rendered the cloning quite uncertain.

– the classical method of immunoscreening the positive clones using previously isolated anti-heparanase antibodies allegedly specific for heparanase would not yield an active product since

these antibodies in fact recognized the protein PA-1. The isolation of novel anti-heparanase antibodies starting from a further purified preparation of heparanase may not have succeeded since the next purification step of the enzyme suggested in document (3) markedly decreased the yield of the protein.

– Had the skilled person chosen the "classical" E.coli or yeast expression systems to identify the enzyme, he/she would have failed since heparanase was synthesized as a proenzyme and proteolytic activation which was absolutely necessary for enzymatic activity would not occur in either of these hosts. Turning to a mammalian expression system would not have been contemplated as no distinction could have been made between endogenous heparanase activity and the activity of the protein encoded by the cloned nucleotide sequence.

– The skilled person would have doubted that the very low heparanase activity observed after cloning in insect cells using a baculovirus vector would be directly attributable to the enzyme since heparanase was known in the art to be extremely active.

It was a significant accomplishment of the inventors that they had overcome all these difficulties and pursued their work to the final characterisation of the enzyme.

VIII. The Appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed at oral proceedings.

Reasons for the Decision

Articles 123(2) and 84 EPC; added subject-matter; clarity, support in the description

1. The basis in the application as filed for the claimed subject-matter is on page 9: lines 1 to 3 in combination with SEQ ID NOS: 10 or 14 (claims 1, 5), on page 8, lines 17 to 38 in combination with SEQ ID NOS: 9 or 13 (claims 2 to 4 and 6), on page 16, lines 29 to 31 (claim 7), on page 9, lines 19 to 21 (claim 8), on page 18 lines 29 to 31 (claim 9), on page 7, lines 27 to 29 (claims 10 and 11), on pages 19 and 20 (claims 12 to 15). The requirements of Article 123(2) EPC are fulfilled.

2. In the Board's judgement, the claimed subject-matter is clearly worded and supported by the description. The requirements of Article 84 EPC are fulfilled.

Article 83 EPC; sufficiency of disclosure

3. Sufficiency of disclosure was never at stake. The Board is also of the opinion that the claimed subject-matter is reproducible on the basis of the information given in the patent specification.

Article 54 EPC; novelty

4. The claims which the Examining Division considered not to be novel have been deleted.

5. There is no prior art document on file disclosing a DNA encoding a polypeptide with heparanase catalytic activity having a sequence sharing at least 70% homology with SEQ ID NOS: 10 or 14. Nor is there on file a document disclosing a DNA comprising a polynucleotide sequence at least 70% homologous with SEQ ID NOS: 9 or 13. The subject-matter of claims 1 and 6, dependent claims 2 to 5, 7 to 9 and of claims 14 and 15 respectively referring back to claims 1 to 7 and to claims 6 or 7 is novel.

6. Claims 10 and 11 (Section V, supra) respectively disclose the pro- and prepro- forms of the heparanase protein (61,191 and 66,407 daltons) as well as functional parts thereof. In contrast, document (3) discloses an uncharacterized heparanase of approximately 50 Kd (cf column 15, lines 58 to 60). As this enzyme is smaller than the claimed pro- and prepro- forms, it is not damaging to the novelty of these forms.

7. The question which remains to be answered is whether or not the mature active enzyme as disclosed in document (3) falls within the definition of "a functional part" of the claimed prepro- or pro- forms characterized by their sequences. The origin of this enzyme is different (human Sk-Hep 1 cells; column 8, lines 15 to 18) from that of the claimed prepro- and pro- forms (expression products of a composite cDNA

originating from Sk-Hep 1 cells, on the one hand and from a placenta Marathon RACE cDNA composite, on the other; page 7 of the application, lines 22 to 36). In addition, in accordance to the Appellants' submissions (passage bridging pages 3 and 4 of the grounds of appeal together with Annex C), it would seem that the protein was never purified to such a state where it could be sequenced. The Board has no reasons to doubt this statement. Indeed, document (3) does not disclose any amino acid sequence. Accordingly, it is concluded that the teaching of document (3) is not detrimental to the novelty of the subject-matter of claims 10 and 11 insofar as it relates to a functional part of the claimed enzymes.

8. The Appellants provided evidence in the form of a declaration (document (10)) that although numerous previous attempts at obtaining the heparanase enzyme had been published before the priority date, none of them had succeeded. In particular, the protein described as heparanase in document (4) on file was later on identified as a low molecular weight chemokine which has no homology to heparanase.

9. For these reasons, the subject-matter of claims 10, 11 and dependent claim 12 is novel. The Board understands claim 13 (Section V, supra) as being directed to a medical device **obligatorily comprising** the novel protein/polypeptide of claims 10 or 11 and, therefore, considers the claim also to be novel.

10. The requirements of Article 54 EPC are fulfilled.

Article 56 EPC; inventive step

Claims 1 and 6

11. The closest prior art is document (3) which is concerned with obtaining a purified preparation of the heparanase enzyme. It discloses a 50Kd heparanase isolated from the human hepatoma cell line Sk-Hep-1, as well as anti-heparanase antibodies. The purification method for the enzyme comprises four chromatographic steps. The resulting purified heparanase is still contaminated with a protein of about the same molecular weight, named PAI-1 (type 1 plasminogen activator inhibitor). The authors advise (cf column 16) that the further removal of PAI-1 may be accomplished by means of Mono-S high pressure liquid chromatography. Alternatively, it is suggested that the material exhibiting heparanase activity eluted from a native polyacrylamide gel following the last purification step could be subjected to amino acid sequencing for the purpose of gene cloning and expression.

12. Starting from document (3), the problem to be solved may be defined as cloning and expressing the gene encoding heparanase as an alternative way to produce the enzyme. As this problem is already clearly identified in said document, its formulation *per se* does not require an inventive step.

13. The solution provided is the DNA of claims 1 or 6 defined by its homology to specific DNA sequences (SEQ ID NOs: 9 or 13) or, alternatively, as encoding a polypeptide itself defined by its homology to the specific amino acid sequences (SEQ ID NOs: 10 or 14)

derivable from SEQ ID NOs: 9 or 13 in accordance with the genetic code as well as its various uses.

14. As it was obvious to attempt the cloning of the heparanase gene (point 12, supra), the questions which remain to be answered are whether on the basis of the knowledge then available to him/her, the skilled person would have had a reasonable expectation of success when attempting to clone the heparanase gene, and whether on the basis of the technical circumstances of the case as now known, it could be expected that he/she would have succeeded in his/her endeavour.

15. In order to establish that the heparanase gene had been cloned, the activity of the cloned gene product would have to be tested. As mentioned by Dr Pecker in her declaration of 9 June 2003 (cf document (10)), the skilled person would refrain from using a mammalian cell line as a host for gene expression because it would result in the problem of being unable to distinguish heparanase activity due to the product of the transfected heparanase gene from that of native heparanase present in most commonly used mammalian cell lines. The skilled person would also be doubtful that heparanase activity could be obtained in other standard expression systems, such as bacteria or yeasts, since these systems would not be expected to carry out the post-translational modifications necessary for a mammalian protein to be active.

16. After the priority date, the anti-heparanase antibodies disclosed in document (3) were shown to be specific for a protein other than heparanase: PA-I (declaration of Dr Vlodavsky of 12 June 2003, document (9), page 2).

This implies that the skilled person using the cloning method well-known at the priority date (see, for example, document (1)) involving ëgt11 as a vector whereby the clones expressing heparanase would be detected by immuno-screening with anti-heparanase antibodies, would never have obtained a cloned DNA fragment encoding an enzyme with heparanase activity.

17. Finally, the pro-heparanase is now known to be divided in three sections: an 8Kd section, a 6Kd section and a 45Kd section, heparanase activity resulting from the removal of the 6Kd section and the linkage of the other two. A specific activating protease is involved in this mechanism which would most probably not be present in cells other than the ones naturally producing active heparanase (ie. mammalian cells unsuitable as host cells, see point 16, supra) (Dr Pecker's declaration, document (10), page 6).

18. For these reasons, the Board is convinced that the skilled person would not have had a reasonable expectation of success when cloning and expressing the heparanase gene on the basis of the very scanty indications in document (3) as regards the possibility of cloning and expressing said gene (cf. point 15, supra). Furthermore, the technical circumstances were such (cf. points 16 and 17, supra) that he/she would not have been able to arrive in a straightforward and obvious manner at the DNA sequences referred to in the present claims.

19. The subject-matter of claims 1 and 6, of dependent claims 2 to 5, 7 to 9 and of claim 15 referring back to claims 6 or 7 is inventive.

Claims 10 and 11

20. These claims relate to the heparanase protein in pro- or prepro- forms characterized by the specific amino acid sequences SEQ ID NOs: 10 or 14. These could only be obtained once the cloning and expression of the full-length cDNAs of claims 1 and 6 was achieved. As these DNAs were found to be inventive, inventive step is also acknowledged to said proteins. The same is true for the pharmaceutical preparation, medical device and heparanase overexpression system of claims 12 to 14 which comprise the protein/polypeptide of claims 10 and 11.

21. The requirements of Article 56 EPC are fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division with the order to grant the patent with the claims of the main request filed during the oral proceedings.

The Registrar: The Chairman:

A. Wolinski L. Galligani