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Datasheet for the decision of 10 May 2007

Case Number: T 1452/06 - 3.3.08

Application Number: 01964964.9

Publication Number: 1309676

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Language of the proceedings: EN

Title of invention:
Human epithin-like serine protease

Applicant:
Bayer HealthCare AG

Opponent:
-

Headword:
Serine protease/BAYER

Relevant legal provisions:
EPC Art. 57
EPC R. 23(e)(3)

Keyword:
"Main request - industrial applicability (no)"

Decisions cited:
T 0338/00, T 0870/04, T 0898/05

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1452/06 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 10 May 2007

Appellant: Bayer HealthCare AG
D-51368 Leverkusen (DE)

Representative: Spaltmann, F.
Bayer HealthCare AG
D-51368 Leverkusen (DE)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 7 June 2006 refusing European application No. 01964964.9 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: P. Julià
M. R. Vega Laso

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division dated 7 June 2006, whereby the European patent application No. 01 964 964.9, which originated from an international application published as WO 01/96378, was refused pursuant to Article 97(1) EPC.

II. The decision of the examining division was based on a main request filed on 23 April 2005 and two auxiliary requests filed on 22 March 2006. The examining division considered that the main request and the first auxiliary request contravened Article 123(2) EPC and that the second auxiliary request did not fulfil the requirements of Article 56 EPC. In its decision, the examining division noted in a remark that the second auxiliary request was also considered to lack industrial applicability (Article 57 EPC).

III. With its letter dated 7 September 2006, the appellant filed a statement setting out the grounds of appeal. The appellant maintained the requests underlying the decision under appeal.

IV. The examining division did not rectify its decision and, pursuant to Article 109(2) EPC, remitted the appeal to the Boards of Appeal.

V. The appellant was summoned to oral proceedings. The summons was sent together with a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal (RPBA), wherein the board expressed its preliminary opinion on the relevant issues,

including the issue of industrial applicability (Article 57 EPC).

VI. With its letter dated 5 April 2007, the appellant filed a new main request and an auxiliary request.

VII. By a fax dated 4 May 2007, the board introduced document B (*infra*) into the appeal proceedings.

VIII. Oral proceedings took place on 10 May 2007. At the oral proceedings, and in support of its argumentation, the appellant filed several documents, including document C (*infra*). After the discussion, the appellant withdrew the auxiliary request.

IX. Claims 1, 4 and 5 of the **main** and sole **request**, which consisted of five claims, read as follows:

"1. An isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 24."

"4. A substantially purified polypeptide comprising a polypeptide characterized by SEQ ID NO: 24."

"5. A method of screening for agents which regulate the activity of a serine protease polypeptide, comprising the steps of:

a) contacting a test compound with a serine protease polypeptide encoded by any polynucleotide of claim 1; and

b) detecting a serine protease activity of the polypeptide, wherein a test compound which increases

the serine protease activity is identified as a potential therapeutic agent for increasing the activity of the serine protease polypeptide, and wherein a test compound which decreases the serine protease activity of the polypeptide is identified as a potential therapeutic agent for decreasing the activity of the serine protease polypeptide."

Claim 2 was directed to an expression vector containing any polynucleotide of claim 1, and claim 3 to a host cell containing the expression vector.

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

A: M.G. Kim et al., Immunogenetics, May 1999, Vol. 49(5), pages 420 to 428 (cited in the application);

B: S. Cal et al., Proc. Natl. Acad. Sci. USA, 5 August 2003, Vol. 100(16), pages 9185 to 9190 (introduced into the appeal proceedings by the board);

C: Prosite, PDOC00124 (introduced into the appeal proceedings by the appellant).

XI. The appellant's arguments on industrial applicability may be summarized as follows:

Article 57 EPC stated that an invention was susceptible of industrial application if it could be made or used in any kind of industry. It was established case law of the Boards of Appeal and normal practice of the EPO, that the requirement of industrial applicability had to

be broadly interpreted. In line therewith, the Boards had acknowledged the industrial applicability of targets or research tools (cf. T 338/00 of 6 November 2002) and of compounds for which only a broad biological activity was known (cf. T 898/05 of 7 July 2006).

Targets are made and commercialized within the pharmaceutical industry. Novel targets were usually identified as being members of a biochemical (druggable) class, such as enzymes, proteases, receptors, channels, etc and by their tissue-expression profile or tissue distribution. About 50% of successful targets were expressed in three or more tissues. Although a profitable use in the sense of commercial success was not required by Article 57 EPC, evidence was nevertheless on file showing the commercial relevance of these targets. They were used in the screening of numerous compounds for identifying new drugs and were an integral part of the industrial process of drug development.

The present application disclosed a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 24. This polypeptide was identified as a serine protease that could be used as a target for screening new drugs applying the methods of screening disclosed in the application. The possible biological functions of this serine protease and the therapeutic relevance of drugs identified by these screening methods, particularly in cancer and in inflammatory diseases, were also explicitly referred to in the application. The anti-proliferative effect on colon cancer cells shown in Example 7 supported the

functions predicted in the application. The expression profile of the identified serine protease was disclosed in Example 9. The broad tissue distribution of this serine protease made it of industrial interest. Moreover, its high expression in specific tissues confirmed a role in the functions mentioned in the application. Although the probe used in Example 9 was derived from SEQ ID NO: 10, it was implicitly disclosed that this sequence and SEQ ID NO: 24 were derived from a single transcript, since the application consistently referred to a single serine protease and not to two different serine proteases. The overall disclosure of the application, including the information and the results provided by the examples, distinguished the present invention from other applications, where the biological function of the disclosed polynucleotides, polypeptides and proteins was only vaguely or incompletely understood (e.g. T 870/04 of 11 May 2005). In the present case, the industrial applicability of SEQ ID NO: 24 was clearly shown in the application as required by Article 57 EPC and Rule 23e(3) EPC.

According to document C, the presence of both the serine and the histidine active site signatures in the polypeptide of amino acid sequence SEQ ID NO: 24 identified, in a clear and unambiguous manner, this polypeptide as a member of the trypsin family of serine proteases. The polypeptide of amino acid sequence SEQ ID NO: 24 was also characterized as a type II transmembrane serine protease closely related to the mouse epithin disclosed in document A. Therefore, the polypeptide of SEQ ID NO: 24 was also defined as a member of the group of epithin-like serine proteases, which included human matriptase. Although not necessary

for defining a target, this information further supported the biological relevance and pharmaceutical interest of the compounds identified by applying screening methods that relied on the epithin-like type II transmembrane serine protease of SEQ ID NO: 24 as a target.

The post-published document B demonstrated that the predictions made in the application were not speculative but technically sound and completely correct. This document showed that SEQ ID NO: 24 and 10 were derived from a single transcript (polyserase-I) that produced two active serine proteases, namely serase-1 (SEQ ID NO: 24) and serase-2 (SEQ ID NO: 10). GST-fusion proteins showed that serase-1 was active as a fused protein. The presence of an unrelated fused protein did not eliminate or modify the protease activity of the serine protease domain (serase-1). Although the specific biological function of polyserase-I, and in particular of serase-1, was not disclosed in document B, relevant roles of this protease in several biological processes were indicated. Thereby, the document supported the use of this serine protease as a target for screening methods in the development of new drugs of therapeutic interest. The post-published document B thus supported the disclosure of the application.

XII. The applicant (appellant) requested that the decision under appeal be set aside and that a patent be granted in the following version: main request (claims 1 to 5) filed on 5 April 2007.

Reasons for the Decision

The disclosure of the application concerning SEQ ID NO: 24 as a serine-protease with several therapeutic indications

1. The claimed subject-matter relates to polynucleotides encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 24, polypeptides characterized by this amino acid sequence and a method of screening for agents which regulate the activity of a serine protease polypeptide of SEQ ID NO: 24 (cf. point IX *supra*).

2. The application describes the polypeptide of sequence SEQ ID NO: 24 as being related to mouse epithin, a type II membrane serine protease, and having an epithin-like serine protease activity. In fact, SEQ ID NO: 24 is defined as "*an extended amino acid sequence of human epithin-like serine protease*" (cf. page 12, lines 7 and 8 and page 83, lines 15 and 16). Whereas the mouse epithin sequence (SEQ ID NO: 11) has 902 residues, sequence SEQ ID NO: 24 has only 549 and therefore, the nucleic acid sequence SEQ ID NO: 25 encoding the polypeptide of SEQ ID NO: 24 is described in the application as a partial sequence of an unknown full-length epithin-like gene (cf. page 18, lines 26 to 27). There is, however, no information as regards the source of sequence SEQ ID NO: 24 or of a polynucleotide encoding a polypeptide of sequence SEQ ID NO: 24, such as sequence SEQ ID NO: 25. It is simply not known whether this latter sequence has been obtained by a search of human genome databases (computer-assisted method) or else by screening human cDNA libraries (wet-lab method).

3. The application further discloses methods for measuring the epithin-like serine protease activity and for screening and identifying modulators of this activity (cf. page 41, lines 7 to 26, page 48, lines 9 to 16 and page 64, line 1 to page 65, line 15). The polypeptide of sequence SEQ ID NO: 24 *"is expected to be useful for the same purposes as previously identified serine proteases ... particularly useful for treating cancer and COPD*" (cf. page 12, lines 10 to 12) and for other therapeutic indications (cf. *inter alia* page 10, lines 13 to 16, page 52, line 24 to page 58, line 19). The basis for all these therapeutic indications is the predicted role of the purported serine protease activity of the polypeptide of sequence SEQ ID NO: 24 in the degradation of the extracellular matrix. Thus, for the claimed subject-matter to fulfil the requirement of industrial application the purported serine protease activity of the polypeptide of sequence SEQ ID NO: 24 is essential.

4. However, no experimental evidence whatsoever is present in the application in support of a serine protease activity for a polypeptide comprising the amino acid sequence of SEQ ID NO: 24. There is no example disclosing this serine protease activity for a polypeptide of sequence SEQ ID NO: 24 nor any evidence showing that the screening methods and the therapeutic indications based on this serine protease activity can actually be achieved with a polypeptide of sequence SEQ ID NO: 24. The question arises thus as to whether, in the absence of this experimental evidence, the application provides enough support for the assumption that the polypeptide of sequence SEQ ID NO: 24 has a

serine protease activity. This support might be provided by a (computer-assisted) comparison of the sequence SEQ ID NO: 24 with sequences of known serine proteases and, more particularly, with the allegedly closely related sequence of epithin disclosed in document A, a document explicitly cited in the application (cf. page 83, line 16).

5. Contrary to appellant's opinion, in the present case it is not necessary to decide on the industrial applicability of research tools nor on the scope of interpretation of the requirements for industrial applicability (cf. T 898/05, *supra*, points 1 to 12 of the Reasons). Rather, the relevant question at issue is the probative value of computer-associated sequence comparison methods and the conclusions derived therefrom, which in accordance with decision T 898/05 (*supra*, point 22 of the Reasons), have to be examined "*on a case-by-case basis regarding the nature of the invention and the prior art relating thereto*".

Probative value of the prior art for the alleged serine protease activity of the polypeptide of sequence SEQ ID NO: 24

6. There is no information in the application as regards the degree of identity or homology of the sequence SEQ ID NO: 24 with other serine proteases or with the multidomain mouse epithin. Nor does the application identify any conserved signatures within the sequence SEQ ID NO: 24 let alone comment on their possible relevance. This information, however, might be obtained by a straight (computer-assisted) comparison of the sequence SEQ ID NO: 24 with the sequence of mouse epithin disclosed in document A (cf. page 423, Figure 3

in document A, and SEQ ID NO: 11 in the application), a document which also identifies the domains and conserved signatures present in the mouse epithin. When carrying out this comparison, it is possible to identify in sequence SEQ ID NO: 24 a serine protease domain that includes a serine (GDSGGP, residues 385 to 390) and histidine (VSAAHC, residues 239 to 244) active site signatures.

7. These serine and histidine active site signatures are identified in the predicted catalytic domain of the mouse epithin when discussing the multidomain structure of this protein in document A. In this context, it is also stated that "*all members of the trypsin family of serine proteases contain these sequences ... If a protein contains both ... motifs in the catalytic domain, the probability of it being a trypsin family serine protease is 100% (Prosite, PDOC00124)*" (cf. page 424, right-hand column, first full paragraph) - this latter document (Prosite, PDOC99124) corresponding to document C in the present proceedings. Accordingly, mouse epithin is defined as a **putative** serine protease. However, document A does not provide any experimental evidence in support of this serine protease activity nor of any other activity at all. The activity of mouse epithin is based only on computer-assisted sequence comparisons. Therefore, the probative value of document A as regards the serine protease activity of sequence SEQ ID NO: 24 does not go far beyond the application itself.

8. Although document C states in fact that, if a protein includes both the serine and the histidine active site signatures, the probability that this protein is a

member of the trypsin family of serine proteases amounts to 100%, this information does not say anything on the actual protease activity of the particular protein. Whereas the presence of these signatures might well be **necessary** for serine protease activity, these signatures are certainly not **sufficient** for a polypeptide to be functionally active. In fact, many of the members of the trypsin family listed in document C are produced as inactive proenzymes (zymogens) that require post-translational processing for their activation (proteolytic cleavage). Nothing is disclosed in the application for sequence SEQ ID NO: 24 nor in document A for mouse epithin. It is not known whether mouse epithin as disclosed in document A (and as SEQ ID NO: 11 in the present application) has serine protease activity or whether post-translational processing is required for achieving this activity, if at all. Likewise there is no information in the application as regards sequence SEQ ID NO: 24, which is the specific sequence used in the screening method of claim 5 (which reads "*comprising*" and thus includes sequences even longer than sequence SEQ ID NO: 24).

9. It has also been argued that the identification of sequence SEQ ID NO: 24 as a member of the type II membrane serine proteases, a subgroup within the family of serine proteases to which mouse epithin belongs, provides further support for the purported serine protease activity of SEQ ID NO: 24 (cf. point XI *supra*).

10. The board notes, first of all, that there is no identification in document C of type II membrane serine proteases as a particular subgroup of serine proteases with shared properties. Secondly, although document A

explicitly refers to enterokinase (cf. page 426, paragraph bridging left-hand and right-hand columns), a multidomain type II membrane serine protease (EC 3.4.21.9, enteropeptidase), document A does not refer to this protease as being a member of a particular subgroup of serine proteases nor does it draw any conclusions therefrom. Thirdly, document A does not elaborate on the possible similarities and differences between the mouse epithin and other cell surface proteins having a N-terminus inside the cell membrane (type II membrane proteins) and a protease activity in their extracellular domains (cf. page 424, left-hand column, lines 3 to 20). No information is given on the mechanisms of production and post-translational processing nor on whether these mechanisms are shared by all type II membrane proteases or whether they are specific for each of them. It is simply not known whether type II membrane proteases are active when anchored in cell surface or whether their activity is only present after further processing, be it by proteolytic cleavage, which might or might not result in the secretion of an active protease, or by any other modification, such as the association or coupling with other proteins to form homodimers or heterodimers.

11. It follows from the above that neither the more general cited prior art related to the serine protease family nor the more specific prior art concerned with type II membrane serine proteases and, more particularly, with mouse epithin, allow any prediction of a serine protease activity for the polypeptide of sequence SEQ ID NO: 24. No probative value can be thus derived from data obtained by comparison with the prior art using computer-assisted methods, and no conclusions can be

drawn from the application as regards a serine protease activity of a polypeptide of sequence SEQ ID NO: 24. The disclosure of this sequence is at best a first step towards the characterization of the full-length gene and the determination of possible post-translational and activation processing which might be required for obtaining an active serine protease.

Post-published document cited as alleged confirmatory evidence

12. It has been argued that the sequence SEQ ID NO: 24 corresponds to a partial sequence of human polyserase-I, a polyprotease described in post-published document B (cited as expert opinion) that generates three independent serine proteases from a single transcript.

13. In fact, the first 490 residues of sequence SEQ ID NO: 24 are identical to the corresponding first 490 residues of polyserase-I, which include a short cytoplasmic domain, a transmembrane domain, a LDL receptor domain, the first trypsin-like serine protease domain (serase-1) and the amino acid residues linking this first protease domain to the second serine protease domain (serase-2). However, 59 residues at the C-terminal end of sequence SEQ ID NO: 24 are completely different from the ones present in the corresponding polyserase-I sequence. The relevance of this difference with regard to the serine protease activity is unknown. It should be noted that, whereas document B refers to the active form of serase-1 after proteolytic cleavage at positions Arg-202 and Arg-503 (cf. page 9188, right-hand column, lines 4 to 6), the latter residue is missing in sequence SEQ ID NO: 24. The absence of this residue in sequence SEQ ID NO: 24 might result in

altered post-translational processing (if at all) and production of a mature protein with properties different from those of serase-1. The presence of splice variants is also reported in document B, although their activity was not analyzed (cf. page 9190, right-hand column, lines 1 to 4).

14. The disclosure in document B of serine protease activity for a recombinant fusion protein with GST and serase-1 does not support appellant's argumentation either. This recombinant fusion protein is produced in a soluble form and not anchored in the cell surface. Moreover, as for other GST-fusion proteins, an apparent autoactivation with proteolytic release of the catalytic domain is observed after incubation at 37°C (cf. page 9187, right-hand column). There is however no evidence on file showing that the polypeptide of sequence SEQ ID NO: 24 might be soluble or result in a soluble form. Nor that the 59 residues at its C-terminus (which are different from the ones of polyserase-I and completely unrelated to GST) will be processed in the same manner as the fusion proteins disclosed in document B.

15. Thus, no conclusions can be derived from document B as regards the serine protease activity of a polypeptide of amino acid sequence SEQ ID NO: 24. If any conclusion is to be drawn, then it is the importance of post-translational processes for achieving the active mature serase-1.

Probative value of the prior art for the alleged biological function and therapeutic indications of the polypeptide of sequence SEQ ID NO: 24

16. It has also been argued that, although no experimental evidence has been provided for serine protease activity of a polypeptide of sequence SEQ ID NO: 24, the structural identification of this polypeptide as being a member of a family of proteins with known industrial interest, namely the family of serine proteases and the subgroup of type II membrane serine proteases, provides enough support for industrial applicability (cf. point XI *supra*). This may be the case under certain conditions (cf. T 898/05, *supra*, point 27 of the Reasons), which however are not given in the present application and particularly not for the claimed subject-matter.

17. First, all (therapeutic or screening) uses mentioned in the application rely on a purported serine protease activity that is predicted to play a role in the degradation of extracellular matrix. However, as stated above, there is no evidence on file showing this activity for a polypeptide of sequence SEQ ID NO: 24. Second, although the polypeptide of sequence SEQ ID NO: 24 has some structural features shared by members of the serine protease family, not all members of this family have the same biological function. The list of proteases of the trypsin family in document C shows the large variety of possible biological functions in which these members might be involved, such as blood coagulation, food digestion, inflammation and immune responses, etc. The mere citation of all these possible functions or an arbitrary (i.e. not based on technical

support) selection thereof relies on mere speculation. Third, in the present case, this support cannot be derived from the allegedly closest structurally related protein, i.e. epithin.

18. Document A states that epithin "*might have several biological or biochemical functions*" and the authors of this document "***suspect*** *it will target either an extracellular matrix or another membrane bound protein on the same or neighbouring cells. In the latter case, epithin cleavage products could activate target cells, facilitating their differentiation, migration, or function*" (emphasis added by the board) (cf. page 426, paragraph bridging left and right-hand columns and page 427, left-hand column, last paragraph). Support for all these suggestions is based only on sequence homology with other serine proteases.

19. Yet, more than four years after the publication of document A and after the subsequent description of a matriptase subgroup of type II transmembrane serine proteases (TTSPs), to which both epithin and polyserase-I belong, the authors of document B state that "*further studies will be required to establish* ***putative*** *functional connections of polyserase-I to matriptases or other members of the growing TTSP protease family. In this regard, it is remarkable that the physiological roles of most TTSPs are still* ***unclear***" (emphasis added by the board) (cf. page 9190, right-hand column). This is a far cry from a well established biological function for these TTSPs on which to base a possible function for the polypeptide of sequence SEQ ID NO: 24. This is all the more so, as references to human matriptase and the matriptase

subgroup of TTSPs can only be made with the benefit of hindsight. Neither human matriptase nor a matriptase subgroup of TTSPs were known to the authors of document A. Nor is any indication thereto in the present application.

Appellant's further arguments on industrial applicability

20. It has been further argued that the experimental results disclosed in the examples of the application, in particular the tissue-specific expression profile (Example 9) and the anti-proliferating effect on colon cancer cells (Example 7), support an industrial applicability for the claimed subject-matter (cf. point XI *supra*).

21. As regards Example 9 concerning the tissue-specific expression profile (cf. page 81, line 4 to page 83, line 13 and Figures 4 and 5), the probe used for determining the expression profile is, according to the appellant, derived from sequence SEQ ID NO: 10. There is however no indication in the application that links this sequence to sequence SEQ ID NO: 24. The application is completely silent on the source of the two sequences, SEQ ID NO: 10 and SEQ ID NO: 24, (genomic or cDNA library, cf. point 2 *supra*) and it does not suggest any possible relationship between them. To recognize the two sequences as encoding independent protease domains of a single transcript (serase-1 and serase-2 of polyserase-I) requires the benefit of hindsight. Hindsight would be thus required for applying possible interpretations and conclusions drawn from the tissue expression profile of sequence SEQ ID NO: 10 to sequence SEQ ID NO: 24.

22. Example 7 shows an anti-proliferative effect on colon cancer cells of an antisense sequence of 24 bases complementary to the nucleotides at position 1 to 24 of sequence SEQ ID NO: 25 (cf. page 70, line 5 to page 71, line 2). These positions correspond to the putative cytoplasmic domain at the N-terminal end (residues 1 to 8) of sequence SEQ ID NO: 24 and far away from the putative extracellular serine protease domain (residues 190 to 433) of sequence SEQ ID NO: 24 or of polyserase-I (cf. document B, page 9186, right-hand column, lines 24 and 25). There is no information in the application nor on file concerning the relevance of this putative cytoplasmic domain, such as its homology with other type II membrane serine proteases, cell-anchored (multidomain) proteases or cell-anchored proteins. Although Example 7 refers to a "*significantly reduced expression of human epithin-like serine protease*", there is no characterization of this epithin-like serine protease nor an indication of the actual specificity of the antisense used, i.e. whether the anti-proliferative effect is due to a specific reduction of expression of a polypeptide of sequence SEQ ID NO: 24, to an inhibition of other epithin-like serine proteases (polyserase-I, matriptase) or other (unrelated, cell-anchored) proteins. In the absence of this information, the relevance of Example 7 for industrial applicability remains at least questionable.

Conclusion

23. A basic principle of the patent system is that exclusive rights can only be granted in exchange for a full disclosure of the invention, which includes the

need to indicate how to exploit the invention (Article 57 EPC). This indication must have "*a sound and concrete technical basis*", as a "*speculative indication of possible objectives that might or might not be achievable by carrying out further research with the tool as described is not sufficient for fulfilment of the requirement of industrial applicability*" (cf. T 898/05, supra, point 5 of the Reasons and T 870/04, *supra*, points 21 and 22 of the Reasons). The only use of a polypeptide of sequence SEQ ID NO: 24 is to find out more about the polypeptide itself and its natural function(s). No "*immediate concrete benefit*" within the meaning of decision T 898/05 (*supra*, point 6 of the Reasons) can be acknowledged for this use.

24. Therefore, the request at issue does not fulfil the requirements of Article 57 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski C. Rennie-Smith