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Case Number: T 0134/23 - 3.3.08

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Language of the proceedings: EN

Title of invention:
NOVEL VERTEBRATE CELLS AND METHODS FOR RECOMBINANTLY EXPRESSING A POLYPEPTIDE OF INTEREST

Patent Proprietor:
Novartis AG

Opponent:
Strawman Limited

Headword:
Methods for recombinantly expressing a polypeptide of interest/ NOVARTIS

Relevant legal provisions:
EPC Art. 54, 56, 83

Keyword:
Main request and auxiliary requests 1 to 8 - Inventive step - (no)
Auxiliary request 9 - Novelty - (no)
Auxiliary request 10 - requirements of the EPC met (yes)

Decisions cited:
T 1818/12, T 0116/18

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 0134/23 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 14 May 2025

Appellant: (Opponent)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Representative:	Harding, Charles, T. Gallon, Matthew O'Brien, Simon D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted/ electronically transmitted on 18 November 2022 concerning maintenance of the European Patent No. 3137595 in amended form**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	D. Pilat
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 3 137 595 is based on European patent application No. 15 739 327.3, filed as an international application published as WO 2015/166427. The patent was opposed on the grounds of Article 100(a) EPC in conjunction with Articles 54 and 56 EPC, and of Article 100(b) and (c) EPC. The opposition division held that the main request (filed on 5 October 2022) fulfilled the requirements of the EPC. It also decided to admit auxiliary requests 1 to 12, filed on 5 October 2022, into the proceedings.

II. The opponent (appellant) lodged an appeal against the decision of the opposition division.

III. With its statement of grounds of appeal, the appellant submitted arguments as to why the claims of the main request and of auxiliary requests 1 to 12 were insufficiently disclosed and lacked novelty, while the claims of the main request, auxiliary requests 2 to 4, 6 to 8 and 10 to 12 lacked an inventive step.

IV. With their reply to the statement of grounds of appeal, the patent proprietor (respondent) submitted arguments as to why the claims of the main request and of auxiliary requests 1 to 12 complied with the requirements of the EPC.

V. In a communication under Article 15(1) RPBA, the parties were informed of the board's provisional opinion on some issues of the case.

VI. The claims of the main request are the claims that were found allowable by the opposition division. Claim 1 of the main request reads as follows:

"1. A method for recombinantly producing a polypeptide of interest, comprising
(a) culturing vertebrate host cells under conditions that allow for the expression and secretion of the polypeptide of interest into the cell culture medium, wherein the vertebrate host cells are isolated vertebrate cells suitable for recombinant expression of a polypeptide of interest, wherein the vertebrate cells are altered to impair the effect of matriptase, wherein the effect of matriptase is impaired because functional expression of the matriptase gene is reduced or eliminated in said cells by gene knock-out, gene mutation, gene deletion, gene silencing or a combination of any of the foregoing, and wherein the vertebrate cells comprise at least one heterologous polynucleotide encoding a polypeptide of interest, wherein the vertebrate cells secrete the polypeptide of interest;
(b) isolating the polypeptide of interest from the cell culture medium; and
(c) processing the isolated polypeptide of interest."

VII. Claim 1 of **auxiliary request 1** differs from claim 1 of the main request in that the vertebrate (host) cells are limited to mammalian (host) cells.

VIII. Claim 1 of **auxiliary request 2** differs from claim 1 of auxiliary request 1 in that the mammalian cells in step a) are further defined as

"wherein the isolated mammalian cells are
(i) rodent cells,

(ii) human cells selected from the group consisting of HEK293 cells, MCF-7 cells, PerC6 cells, CAP cells, human hematopoietic cells and HeLa cells, or (iii) monkey cell selected from the group consisting of COS cells, COS-1 cells, COS-7 cells and Vero cells".

IX. Claim 1 of **auxiliary request 3** differs from claim 1 of the main request in that the vertebrate (host) cells are limited to rodent (host) cells.

X. Claim 1 of **auxiliary request 4** differs from claim 1 of the main request in that the vertebrate (host) cells are limited to CHO (host) cells.

XI. Claim 1 of **auxiliary requests 5 to 8** differs from claim 1 of auxiliary requests 1 to 4, respectively, in that it additionally includes at the end of step (a) "and wherein the polypeptide of interest is susceptible to clipping by proteases".

XII. Claim 1 of **auxiliary requests 9 to 12** differs from claim 1 of auxiliary requests 1 to 4, respectively, in that it additionally includes at the end of step (a) ", wherein the polypeptide of interest is susceptible to clipping by proteases, and wherein impairing the effect of matriptase in said cell reduces or eliminates clipping of the secreted polypeptide of interest".

XIII. The documents cited in this decision include the following:

D1 T.G. Warner, Glycobiology, vol. 9, pages 841 to 850, 1999

D2 K. List *et al.*, Oncogene, vol.21, pages 3765 to 3779, 2002

D3 A.J. Najy *et al.*, Mol. Cancer Res. vol. 10(8), pages 1087 to 1097, 2012

D4 Y-W. Chen *et al.*, J Med Sci, vol 32(3), pages 97 to 108, 2012

D5 A. Welman *et al.*, PLoS ONE, vol. 7, issue 4, e34182 pages 1 to 11, 2012

D7 E.B. Clark *et al.*, J. Biol. Chem., vol. 285(35), pages 27130 to 27143, 2010

D11 C. Tans *et al.*, Animal Cell Technology, pages 295 to 300, M. J. T. Carrondo *et al.* (eds.), Springer 1997

D16 D. Baycin-Hizal *et al.*, J. Proteome Res., vol. 11(11), pages 5265 to 5276, 2012

D17 Supplementary table 2 of D16

D18 S. Netzel-Arnett *et al.* Cancer and Metastasis Reviews vol.22, pages 237 to 258, 2003

XIV. The parties' submissions, insofar as they are relevant to the decision, are discussed in the Reasons for the Decision, below.

XV. The parties' final requests, insofar as relevant for the present decision, were the following:

The appellant requested that the decision under appeal be set aside and the patent be revoked in its entirety.

The respondent requested that the appeal be dismissed (main request) or that the appealed decision be set aside and the patent be maintained on the basis of one of auxiliary requests 1 to 12 filed on 5 October 2022.

Reasons for the Decision

Main request

Novelty (Article 54 EPC)

1. In the appealed decision, the opposition division came to the conclusion that claim 1 of the main request was novel over documents D3 and D7. In appeal, the appellant contested this conclusion and maintained their novelty objections.

2. The board maintains its preliminary opinion, provided in section 32 of the communication pursuant to Article 15(1) RPBA, that claim 1 of the main request lacks novelty over document D3. However, for procedural efficiency reasons, at oral proceedings the board decided to start discussing inventive step (with document D1 as closest prior art) rather than novelty over D3 and only discussed novelty for auxiliary request 9, after having concluded that all higher ranking requests lacked inventive step. Hence in the present decision, a reasoned decision on novelty is given only for auxiliary request 9, although it is readily apparent that the same objection also applies to claim 1 of the main request and of auxiliary requests 1 and 5 (see below).

Inventive step (Article 56 EPC)
Closest prior art and distinguishing features

3. The board considers that the disclosure of document D1, which relates to recombinant protein production in CHO cells and identifies clipping as a major widely

observed problem in recombinant protein production, represents a suitable starting point for the discussion of inventive step of claim 1. This was not disputed.

4. It is also uncontested that the distinguishing feature between D1 and the method of claim 1 is that D1 does not disclose host cells that are altered to impair the effect of matriptase.

Technical effect and objective technical problem

5. With regard to the technical effect associated with this distinguishing feature, the following is noted.

6. The experimental data provided in the patent relate to polypeptides of interest that are not technically characterized beyond their mere generic designations such as antibodies (mAbs), Fc-fusion proteins, and glycosylated viral proteins. As a result, these examples must be regarded as essentially theoretical, since technical details of the method used remain undefined and, consequently, the examples cannot be readily assessed for extrapolation purposes. It is therefore questionable whether the data disclosed in the patent demonstrate a technical effect that can be reliably extrapolated to polypeptides of interest in general. Moreover, all examples of the patent are limited to the use of CHO-K1 cells. The results obtained with matriptase suppression are compared against those obtained with suppression of only a small number of other proteases assessed under narrowly defined conditions. In contrast, claim 1 covers all possible vertebrate cells and all possible polypeptides of interest. Given that such polypeptides may differ in either primary, secondary, and/or tertiary structure, it cannot be established whether they all possess an

accessible matriptase cleavage site susceptible to clipping, nor whether expression in a host cell with an impaired matriptase function would result in a reduction in clipping. Consequently, the board has serious doubts that the technical effect alleged by the respondent - namely reduction of undesirable clipping events of the polypeptide of interest in the cell culture medium, resulting in an increased yield and improved quality of intact recombinant polypeptide of interest - is genuinely independent of the presence of at least one cleavage site accessible to matriptase in the polypeptide of interest and is achieved across the whole scope of the claim. Hence, the board comes to the conclusion that no technical effect can be attributed to the distinguishing feature.

7. The respondent essentially argued that the patent credibly shows, by way of its examples, that the claimed method confers advantages in the recombinant production of secreted polypeptides of interest. Whether these advantages would be present regardless of the host cell used and for each and every polypeptide of interest was irrelevant, because these were not the distinguishing features. The host cells according to the invention were better suited for recombinant production of several polypeptides that would otherwise be clipped by matriptase and could also be used for the production of polypeptides that were not subject to clipping. In any case, clipping was a widely observed effect, essentially affecting all proteins, as discussed both in the patent (e.g. paragraph [0004]) and in D1. The reduction or elimination of expression of matriptase in the host cell was described as resulting in a significant reduction, or even complete elimination, of clipping of secreted recombinant polypeptides of interest in the cell culture medium,

thereby leading to an increased yield of intact recombinant polypeptides of interest (patent e.g. paragraphs [0009], [0010], [0018], [0022], [0023]). While serine proteases other than matriptase could be involved in the clipping, the patent showed that knocking down matriptase reduced the risk of clipping, thus resulting in a better production cell line. The respondent referred to decision T 1818/12 (see in particular Reasons 14 to 16), wherein it was concluded that the overall evidence in the patent convincingly demonstrated that using the claimed method led to a technical effect, achievable over substantially the entire claimed scope, although a single set of conditions, falling within the ambit of the claimed subject-matter, did not achieve the effect (e.g. an improved yield of high purity antibodies). Similar conclusions had also been reached in T 116/18 of 28 July 2023, following the rationale of G 2/21, where it had been found that an effect did not have to be shown for all possible insects in order to be found credible.

8. The board is not persuaded by the respondent's arguments. While it was indeed known that protease mediated clipping in the cell culture medium was a major issue in the use of vertebrate, in particular mammalian, cells for secreted recombinant expression, the patent provides no technical teaching allowing to conclude that simply knocking down one of the many possible proteases involved in this process would solve this problem across the whole scope of the claim. Instead the prior art teaches that, because several proteases, including serine proteases, are suspected of being secreted by CHO cells and to be extracellularly active, multiple genetic loci encoding these proteases would need to be controlled (D1, page 842, right-hand

column, first paragraph). While an effect was shown in the patent, in all reported examples the secreted polypeptides of interest are identified by means of their generic structural or functional type (i.e. monoclonal antibody, Fc-fusion protein, glycoprotein variants, therapeutic proteins, monoclonal IgG antibody), which does not permit an assessment of whether the respective polypeptides are sensitive or resistant to matriptase mediated clipping in the producing cell.

9. While the board accepts respondent's view that the specific sequence of the expressed polypeptides of interest does not need to be claimed, when assessing whether the alleged technical effect of reduction of undesirable clipping events of the polypeptide of interest is actually achieved, however, the specific sequence, or at least relevant primary to tertiary structural features of the expressed polypeptides used in the examples cannot be disregarded.

10. Examples 3 and 4 show that matriptase in mouse cells, like its hamster counterpart, is capable of mediating clipping of recombinant polypeptides in the culture medium. However, while these findings suggest that matriptase, or its orthologs, functions as a clipping enzyme for the generically designated polypeptide of interest used in the examples, such observations cannot plausibly be generalised across all polypeptides with differing primary, secondary, and tertiary structures, and vertebrate host cells. On this basis, the board is not persuaded that the asserted technical effect of reduction of undesirable clipping events of the polypeptide of interest necessarily arises from the claimed genetic alteration of the host cell to reduce or eliminate functional expression of the matriptase

gene, nor that such effects are credibly achieved across the full scope of the claim, i.e. on any polypeptides of interest, including polypeptides lacking at least one matriptase accessible cleavage site.

11. Even if the claimed process were intended to only reduce the risk of cleavage of the secreted recombinant polypeptide by addressing a major cause of clipping during the production process, any such reduction, if achieved at all, would depend on several factors, in particular the cell type and the primary to tertiary structure of the recombinant polypeptide. A mere reduction in the risk of clipping or the preservation of favourable growth and expression characteristics is insufficient to establish the alleged technical effect of reduction of undesirable clipping events of the polypeptide of interest, because any reduction in clipping is neither certain nor universal. As acknowledged by the respondent, matriptase cleavage depends on the structural accessibility of the cleavage site. The tertiary structure of the polypeptide, as well as secondary and post-translational modifications, may shield potential clipping sites and thereby modulate its susceptibility to matriptase activity. Hence, these very considerations confirm that the technical effect observed for the generically defined polypeptides in the patent examples cannot be reliably extrapolated to all polypeptides of interest. As a result, it is not credible that this effect is achieved for the vast majority of the polypeptides falling within the scope of the claim.

12. As regards the arguments based on decisions T 1818/12 and T 116/18 (see point 7. above), the board considers that the conclusions in these decisions are not

applicable to the case in hand, since none of the experimental examples disclosed in the present patent establishes in a convincing manner that the claimed method achieves the alleged technical effect for all polypeptides of interest, and thus across the full scope of the claim. The present issue is not that, based on the examples in the patent, one single embodiment falling within the ambit of the claim fails to achieve the effect, but rather that it is not credible that essentially all embodiments, i.e. the vast majority of the polypeptides of interest falling within the scope of the claim, would achieve this effect. This is because the examples in the patent provide only limited technical information regarding the polypeptides of interest, which are defined merely by their generic structural or functional type, such that the alleged effect cannot reasonably be extrapolated therefrom and generalised across the full scope of the claim.

13. Since the technical effect identified above (see point 6.) cannot plausibly or credibly be regarded as being achieved/achievable across the full scope of the claim, the board concludes that it cannot be taken into account when formulating the objective technical problem (Case law of the Boards of Appeal of the European Patent Office 10th edition 2022, hereinafter "Case Law", I.D.4.3.1).

14. The objective technical problem is thus to be formulated as the provision of an alternative method for producing a recombinant polypeptide.

15. The board is satisfied that the method of claim 1 solves this technical problem.

Obviousness

16. Starting from document D1 and faced with the technical problem identified above, the skilled person would not require a pointer or motivation to arrive at the claimed solution. Document D1, Table 1, already identifies extracellular proteases as candidate genes for being controlled by antisense or gene disruption, with the aim of improving recombinant protein production by reducing polypeptide clipping. On this basis, the skilled person would have looked for serine proteases expressed and secreted by CHO cells and have assessed the impact of impairing their activity on recombinant polypeptide expression, without needing to expect that an improvement over the method of D1 would be achieved. Impairment of the serine protease matriptase would be one of many equally plausible alternative solutions to the technical problem posed. By doing so, the skilled person would have arrived at a method according to claim 1 without the exercise of an inventive step.

17. Although there would be no need for a pointer to matriptase, the board notes that matriptase was a well known serine protease with clinical and biological relevance (e.g. D2, Title, abstract; D3, abstract; D4 Title; abstract; D5, page 1, left-hand column, first full paragraph) and had already been listed among other proteins in a study aiming to improve the understanding of recombinant expression in CHO cells and disclose information relevant for targeted manipulation of CHO cellular functions (D16, abstract and page 10, second paragraph, last sentence); matriptase is identified in D16's Supplementary Table 2 (D17, page 11, line 4; see also D6).

18. Thus, the skilled person, aiming at providing alternative host cells for recombinant protein production and knowing from D1 that proteases in the culture medium caused the undesired effect of protein clipping, would have tested and altered the CHO cells in order to impair the functional expression of genes encoding serine proteases, including maptriptase. This could be achieved by gene knock-out, gene mutation, gene deletion, gene silencing or a combination of any of the foregoing.

19. The selection of matriptase would be arbitrary, because, in the absence of any requirement to achieve a specific advantageous effect, the skilled person, starting from D1 and faced with the technical problem identified above, could have selected any of the numerous equivalent serine proteases expressed in CHO cells, among them matriptase. Accordingly, even if matriptase is not pointed to in the prior art, its selection represents only one of several equivalent solutions available to the skilled person at the effective time.

20. Accordingly, the subject-matter of claim 1 of the main request does not fulfil the requirements of Article 56 EPC.

Auxiliary requests 1 to 8

21. Claim 1 of auxiliary request 1 to 8 is identical to claim 1 of the main request except for the differences set out in points VII. to XII. above, namely that the host cells are mammalian cells (auxiliary requests 1, 2, 5 and 6) selected from rodent cells or from two lists of specific human or monkey cells lines (auxiliary requests 2 and 6), or are rodent cells

(auxiliary requests 3 and 7) or are CHO cells (auxiliary requests 4 and 8); a further feature in auxiliary requests 5 to 8 is that - at the end of step (a) - the polypeptide of interest is defined as being susceptible to clipping by proteases.

22. Document D1 likewise relates to methods employing CHO cells and thus the amendment introduced into claim 1 of auxiliary requests 1 to 4 does not impart any further distinguishing feature to the disclosure of document D1. As to the further limitation in auxiliary requests 5 to 8 that the polypeptide of interest must be susceptible to clipping by proteases, not only may this feature be considered implicitly disclosed in D1, it also does not change the assessment of a technical effect, since it relates to clipping by any protease other than matriptase as well, for which no technical effect has been shown to be credibly achievable, neither in the patent nor in the prior art, when the functional expression of the matriptase gene is reduced or eliminated in said cells by gene knock-out, gene mutation, gene deletion, gene silencing or a combination of any of the foregoing.

23. Thus, no technical effect can be associated with any of these additional features, based on which a technical problem and an inventive step could be acknowledged. For these reasons the lack of inventive step reasoning developed above for claim 1 of the main request also applies to auxiliary requests 1 to 8.

Auxiliary request 9

Claim 1 reads as follows:

"1. A method for recombinantly producing a polypeptide of interest, comprising
(a) culturing mammalian host cells under conditions that allow for the expression and secretion of the polypeptide of interest into the cell culture medium, wherein the mammalian host cells are isolated mammalian cells suitable for recombinant expression of a polypeptide of interest, wherein the vertebrate cells are altered to impair the effect of matriptase, wherein the effect of matriptase is impaired because functional expression of the matriptase gene is reduced or eliminated in said cells by gene knock-out, gene mutation, gene deletion, gene silencing or a combination of any of the foregoing, and wherein the mammalian cells comprise at least one heterologous polynucleotide encoding a polypeptide of interest, wherein the mammalian cells secrete the polypeptide of interest, wherein the polypeptide of interest is susceptible to clipping by proteases, and wherein impairing the effect of matriptase in said cell reduces or eliminates clipping of the secreted polypeptide of interest;
(b) isolating the polypeptide of interest from the cell culture medium; and
(c) processing the isolated polypeptide of interest."

Claim construction

24. Step (a) of claim 1 defines a culturing step in which the mammalian host cells secrete the polypeptide of interest. Although not explicitly stated in the claim, the only reasonable interpretation of step (a) of claim 1 is that the recombinantly expressed polypeptide of interest is secreted by the host cells into the cell culture medium. The polypeptide of interest is not limited in any way, except in that it needs to be

susceptible to clipping, including clipping by proteases or by matriptases. The expression "at least one heterologous polynucleotide" simply indicates that the host cells may contain more than one such heterologous polynucleotide encoding a polypeptide of interest, as is confirmed by paragraph [0054] of the patent. Impairing the effect of matriptase covers both permanent and transient reduction or elimination of the endogenous expression of the matriptase gene in the host cells, including transient reduction via gene silencing mechanisms.

25. As to steps (b) and (c), any suitable isolating and processing techniques may be used, provided that, in combination, they result in an isolation and/or a processing of a polypeptide of interest. Step b) may be interpreted as separating the polypeptide of interest from at least some components of the cell culture medium, i.e isolating the polypeptide of interest out of that environment prior to further handling (i.e., step (c) "processing"). Step c) may be interpreted as any step of further manipulating the polypeptide after it has been isolated from the cell culture medium. Finally, the feature "wherein impairing the effect of matriptase in said cell reduces or eliminates clipping of the secreted polypeptide of interest" constitutes a further limitation of the claim. It is not enough to have impaired the matriptase gene; it is also required that clipping of the secreted polypeptide of interest is thereby reduced or eliminated.

Sufficiency of disclosure

26. Article 83 EPC stipulates that the application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person

skilled in the art. According to decision G 1/03 (OJ EPO 2004, 413, reasons 2.5.2), "[i]f an effect is expressed in a claim, there is lack of sufficient disclosure. Otherwise, i.e. if the effect is not expressed in a claim but is part of the problem to be solved, there is a problem of inventive step". Since in the present case the effect of "impairing the effect of matriptase in said cell reduces or eliminates clipping of the secreted polypeptide of interest" is recited in the claim, the board agrees with the appellant that it must be taken into account under sufficiency of disclosure rather than under inventive step.

27. The appellant contended that it would be undue burden to carry out the alleged invention essentially because identifying appropriate polypeptides of interest, namely those susceptible to clipping by matriptase, would require excessive trial-and-error involving any possible polypeptide and there was even no guarantee that any such polypeptides would be identified. The patent did not provide any guiding teaching on how to use any polypeptide in any cell; in fact Figure 1 provided evidence that there was still clipping even when matriptase was impaired. There was also no teaching on how to identify a matriptase cleavage site or how such a site would be exposed to cleavage, while there was evidence on file that such a site may not be accessible for cleavage (D7, page 27138 right column last section). Moreover, the term matriptase was not structurally defined in the claim and in fact appeared to be a generic designation covering many different proteins (patent, paragraph [0024] and Table 1), of which for example HAI was even an inhibitor of matriptase (D3, page 6, second to last line). There were different types of matriptase with similar structures (e.g. paragraph [0024] of the patent; D18,

Figure 1), and the patent indicated that some of these (matriptase-2 and matriptase-3) would not be covered by the term "matriptase" (paragraph [0024]). The term "matriptase" was thus ambiguous and it was not possible for the skilled person to determine whether impairment of matriptase-2 or matriptase-3 fell within the scope of the claims.

28. The board considers that host cells defined as in the claim, namely cells wherein functional expression of matriptase is impaired, can easily be made by the skilled person applying standard techniques. The skilled person can then easily determine, applying standard and routine experiments, whether or not clipping of the polypeptide of interest in the culture medium occurs and can compare the result with that obtained from cells in which no matriptase impairment has been made. As argued by the respondent and not contested by the appellant, most polypeptides are susceptible to cleavage by proteases (D1, D11), and hence the skilled person would only have to identify from among such polypeptides those that show the claimed effect. The patent provides multiple examples on how to identify them (Examples 1 and 4, Figure 1). There is no undue burden to test the polypeptide of interest and identify one claimed cell in which clipping is reduced. This may involve time-consuming work, but only requires use of routine procedures and is not undue burden; the board agrees with the respondent that no serious doubts, supported by verifiable facts, have been provided to demonstrate that the skilled person would be unable to perform the method across the scope of claim 1. Finally, the board considers, in agreement with the respondent, that the arguments concerning the term "matriptase" are in fact clarity objections which do not play a role in the

assessment of Article 83 EPC. In any case, the patent extensively describes what falls under the designation of matriptase (e.g. paragraphs [0021], [0024] and [0025]). If some proteases may be designated matriptase but do not have its function, then their suppression will not result in reduced clipping of the polypeptide of interest, in which case such an embodiment will not form part of the scope of the claim.

29. Consequently, claim 1 of auxiliary request 9 meets the requirements of Article 83 EPC.

Novelty (Article 54 EPC)

30. In the appealed decision, the opposition division came to the conclusion that claim 1 of the main request was novel over D3, because D3 did not disclose at least steps (b) and (c) of claim 1.

31. In appeal, the respondent argued that D3 did not disclose that the polypeptide of interest was secreted into the culture medium, as required by step (a) of claim 1.

32. The board disagrees. Firstly, in D3, human prostate epithelial BPH-1 cells (mammalian cells) are transformed to express PDGF D which is secreted into the cell culture medium and is detectable in the conditioned media, even though said cells are not transformed with a matriptase shRNA construct (page 5, third paragraph, fourth sentence; Figure 1B, right-hand panel). Secondly, D3 shows that the level of total and shed matriptase is reduced in the conditioned medium of the PDGF D transformed BPH-1 cells transduced with matriptase shRNA (page 4, third full paragraph, Fig. 6A). Thirdly, D3 further shows that the shRNA-mediated

inhibition of matriptase suppresses the PDGF D induced phenotypes in PDGF D BPH-1 transformed cells, compared with cells in which matriptase expression is not inhibited. Finally, since the PDGF D dimer is expressed and secreted into the cell culture medium as a latent growth factor and is subsequently activated by clipping through matriptase (D3, page 6, fourth paragraph), any effect observed in PDGF D BPH-1 cells expressing matriptase shRNA can only, in the absence of evidence that inhibition of matriptase abolishes the PDGF D secretion, be attributed to the absence of matriptase-activated forms of PDGF D (D3, Figs. 6B and 6C; page 7, second paragraph, sentences 1 through 3). Consequently, on the basis of the information provided in D3, the skilled person would - beyond doubt - have directly and unambiguously concluded that PDGF D secretion still occurs under these conditions. Hence, the subject-matter encompassed in step (a) of claim 1 is directly and unambiguously disclosed, beyond any doubt, in document D3.

33. As regards step (b) of claim 1, the board considers that, contrary to the decision under appeal and the respondent's arguments and according to the claim interpretation in point 25. above, the step of concentrating the cell culture media using a centrifugal filter unit as disclosed in D3 (page 3, fourth paragraph) is a polypeptide isolation step within the meaning of claim 1, step b), since also (ultra)filtration constitutes a technique for isolating the polypeptide of interest from the cell culture medium as required in step (b) of claim 1. This is supported by paragraph [0084] of the patent, which states that the polypeptide is "recovered from the nutrient medium by conventional procedures including, but not limited to, centrifugation, filtration, ultra-

filtration, extraction or precipitation". According to the claim interpretation in point 25., step b) does not exclude a separation of the secreted PDGF D from components present in the cell culture medium by using an Amicon centrifugal filter unit from Millipore. A separation - to some extent - of the polypeptide of interest from at least some components of the cell culture medium is sufficient. Besides, D3 discloses one single and unique concentration step of the BPH-1 cell culture medium. This step is applied to BPH-1 cell culture medium comprising secreted PDGF D to isolate the conditioned medium (D3, page 3, fourth paragraph). Although D3 does not disclose the detection of PDGF D in Fig.6A, the concentration step applied to the culture medium obtained form BPH-1 cells expressing PDGF D, would, irrespective of whether matriptase expression is knocked down or not, inevitably result in conditioned medium in which the secreted PDGF D is retained on the filter membrane. This conclusion also follows from Fig. 6A of D3, which shows that both matriptase and HAI-1 were retained on the filter membrane. Since matriptase and HAI-1 have molecular weights comparable to that of PDGF D (D3 reports approximately 50 kDa for monomeric PDGF D, 80 kDa for activated matriptase, and 40–50 kDa for HAI-1; see Figure 6A), the filter membrane could not have retained matriptase and HAI-1 without also retaining the secreted PDGF D present in the cell culture medium. From this teaching, it is beyond doubt that the conditioned culture medium used in Fig.6A must comprise an isolated PDGF D molecule.

34. As regards step (c) of claim 1, the board considers that also this processing step is disclosed in D3, since the concentrated media, i.e. the isolated polypeptide, was then transferred onto a membrane by

electrophoresis, i.e. processed, for immunoblot analysis (D3, page 3, fourth paragraph, final sentence). This can be considered to represent a step of processing the isolated polypeptide of interest obtained in step (b), when considering paragraph [0084] of the patent referring *inter alia* to electrophoretic procedures as a further processing step.

35. The respondent argued that steps b) and c) as carried out in D3 are not performed in the context of a method of recombinantly producing a polypeptide of interest according to claim 1. The board considers this argument to be irrelevant as the purpose identified in the preamble of claim 1 merely indicates that the claimed method is suitable for producing a polypeptide of interest. It imposes no further technical functional limitation beyond the process steps defined in claim 1 (Case Law, I.C.8.1.3, part d)).

36. Thus, the board concludes that claim 1 of auxiliary request 9 lacks novelty over document D3 (Article 54(2) EPC).

Auxiliary request 10

37. Claim 1 of auxiliary request 10 differs from claim 1 of auxiliary request 9 in that it further specifies that the mammalian cells are either rodent cells or specific human and monkey cell lines.

Novelty (Article 54 EPC)

38. The appellant has not raised any objections for lack of novelty over D3, and the board notes that the mammalian cells used in D3, BPH-1, are human cells and are not among the list of human cell lines listed in claim 1.

Hence, claim 1 of auxiliary request 10 is novel over D3.

39. With the grounds of appeal, the appellant argued that claim 1 of all claim requests on file lacked novelty over D7. Despite the preliminary opinion of the board in its communication pursuant to Article 15(1) RPBA, according to which document D7 was not novelty destroying for claim 1 of the main request, the appellant did not wish to discuss this issue further at oral proceedings. Hence the board had no reason to change its preliminary opinion. In summary, the board agrees with the appealed decision and the respondent that document D7 is not novelty destroying for the subject-matter of claim 1 of the main request and hence also not for claim 1 of auxiliary request 10, which has more limitations. Contrary to the appellant's arguments, the board considers that document D7 differs from claim 1 at least in that the recombinant transmembrane proteins remain anchored within the membrane of the host cells and are not secreted by the host cells into the cell culture medium as required by claim 1. Appellant's arguments that the extracellular part of an anchored transmembrane protein is directed towards the cell culture medium and therefore also secreted are not convincing, because that is not the normal understanding that a skilled person would give to the term "secreted" into the cell culture medium in this context. Hence, claim 1 of auxiliary request 10 is also novel over document D7.

Inventive step (Article 56 EPC)

40. Although in the grounds of appeal the appellant stated that each of the main request and auxiliary requests 1 to 12 lacked an inventive step when starting from D1 as

closest prior art (page 4 of the grounds of appeal, Executive Summary), this objection was not further substantiated as regards auxiliary request 10. After extensively discussing inventive step in relation to the main request in section 4 of the grounds of appeal, the appellant then continued this discussion in relation to auxiliary requests 2 to 4 (section 4.6.3), 6 to 8 (section 4.6.4) and 10 to 12 (section 4.6.5). However, when discussing auxiliary requests 10 to 12, the appellant merely stated that the claims of auxiliary requests 10 to 12 lack inventive step over D3 for the same reasons as auxiliary requests 6 to 8 (page 124 of the grounds of appeal).

41. Admittance of this objection was contested by the respondent. In its preliminary opinion pursuant to Article 15(1) RPBA, the board had already indicated that it considered that objections of lack of inventive step starting from D3 as closest prior art were a fresh case in appeal and that it did not intend to admit them (items 14. and 36. of the preliminary opinion). At the oral proceedings, the appellant stated that they had no further substantiated objections against auxiliary request 10 (see page 7, paragraph 5, of the minutes of the oral proceedings). Hence, the board has no reasons to change its preliminary opinion and decides not to admit any of the objections on lack of inventive step against auxiliary request 10, either because of lack of substantiation (D1 as closest prior art) or because of being late-filed (D3 as closest prior art). As a consequence, there was no inventive step objection against auxiliary request 10 which had to be decided.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of the claims 1 to 9 of auxiliary request 10 filed on 5 October 2022 and a description and drawings eventually to be adapted thereto.

The Registrar: The Chairwoman:

C. Rodríguez Rodríguez T. Sommerfeld

Decision electronically authenticated