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D E C I S I O N
of 1 July 2004

Case Number: T 0882/01 - 3.3.8

Application Number: 93917891.9

Publication Number: 0651803

IPC: C12N 15/13

Language of the proceedings: EN

Title of invention:
Protein expression system

Patentee:
CELLTECH THERAPEUTICS LIMITED

Opponents:
Genentech, Inc.
Monsanto Company
Chiron Corporation

Headword:
Protein Expression System/CELLTECH

Relevant legal provisions:
EPC Art. 54, 111(1)

Keyword:
"Main request: novelty (no)"
"First auxiliary request: admissibility (yes)"
"Remittal to the first instance (yes)"

Decisions cited:
G 0009/91, T 0455/96, T 0091/98, T 0796/02

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0882/01 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 1 July 2004

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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 2 August 2001 revoking European patent No. 0651803 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
S. C. Perryman

Summary of Facts and Submissions

I. The patentee (appellant) lodged an appeal against the decision of the opposition division given at oral proceedings on 15 March 2001 with written reasons posted 2 August 2001 revoking the European patent No. 0 651 803 which had been granted on European application No. 93 917 891.9.

II. Three parties (opponents 1, 2 and 3) had opposed the patent. They are the present respondents (I, II and III respectively).

III. The patent had been opposed on the grounds, as set forth in Article 100(a) EPC, that the invention was not new (Article 54 EPC) and did not involve an inventive step (Article 56 EPC), and, as set forth in Article 100(b) EPC, that it was not sufficiently disclosed.

IV. The sole reason for revocation given in the decision was lack of novelty of granted claim 1 over document (22) (see section XII, infra). At the oral proceedings before the opposition division, document (32) (see section XII, infra) was introduced into the proceedings but the issue of novelty thereover was not discussed in the decision. The issues of sufficiency of disclosure and inventive step were not even discussed at the oral proceedings before the opposition division.

V. Together with its statement of grounds of appeal dated 6 December 2001 the appellant submitted a main request and three auxiliary requests. The main request exactly corresponded with the claims as granted.

VI. In reply to the statement of grounds of appeal, each of the respondents filed observations.

VII. A communication under Article 11 of the Rules of Procedure of the Boards of Appeal presenting some preliminary and non-binding views of the board was then sent to the parties. It was in particular indicated therein that at the oral proceedings, should any of the auxiliary requests be considered, the question of remittal to the opposition division would be discussed.

VIII. In reply to the board's communication, each of the respondents filed further observations.

IX. The oral proceedings took place on 1 July 2004.

X. Claims 1 and 9 of the main request read respectively:

"1. A method for producing one or more heterologous protein(s) in a bacterial host cell comprising culturing a bacterial host cell transformed with one or more expression vectors comprising one or more heterologous DNA sequences under the control of at least one regulatable promoter, an origin of replication maintaining medium vector copy number and a transcriptional terminator characterised in that said host cell is cultured in a defined medium in the absence of antibiotic selection."

"9. A method according to Claim 1 wherein said heterologous DNA sequence(s) are fused to a DNA sequence encoding a secretion sequence."

XI. Claim 1 of the first auxiliary request read:

"1. A method for producing one or more heterologous protein(s) in a bacterial host cell comprising culturing a bacterial host cell transformed with one or more expression vectors comprising one or more heterologous DNA sequences under the control of at least one regulatab[l]e promoter, an origin of replication maintaining medium vector copy number and a transcriptional terminator characterised in that said host cell is cultured in a defined medium in the absence of antibiotic selection and in that said heterologous DNA sequence(s) are fused to a DNA sequence encoding a secretion sequence."

The rest of the claims of the first auxiliary request (claims 2 to 9) were dependent on claim 1.

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

(22) Gregg Bogosian et al., J. Biol. Chem., Vol. 264, No. 1, 5 January 1989, Pages 531 to 539;

(23) Peter H. Calcott et al., Dev. Ind. Microb., Vol. 29, Suppl. No. 31, 1988, Pages 258 to 266;

(32) Celia A. Caulcott et al., J. Gen. Microb., Vol. 131, 1985, Pages 3355 to 3365.

XIII. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Main request - Novelty of claim 1

Document (22) did not disclose the method of claim 1 for the reason that the cells were grown in the presence of an antibiotic and, anyway, there were no data therein which indicated the copy number of the plasmid present in the cells.

As plasmid pBGH1 encoded resistance to ampicillin and tetracycline, as indicated in document (22) on page 532, left-hand column, the skilled person would have understood that the defined medium in which the fermentations were conducted implicitly contained an antibiotic for maintaining the plasmid in the cells during the growth phase even though there was no explicit mention of the presence of an antibiotic as a component of the medium. In contrast to this, where special circumstances, such as the curing of pBGH1 reported in the Chapter entitled "Curing of pBGH1 from W3110G" on page 532, right-hand column, required that no antibiotic should be used, the absence of an antibiotic in the medium used was expressly pointed out.

Document (23), which was cited in document (22), reported that the pBGH1 plasmid was determined to be present in the range of 30 to 35 copies per cell. However this determination was made in the presence of an antibiotic. It could not be deduced from this that plasmid pBGH1 in the absence of antibiotic was present in cells at a medium copy number.

Whereas a method for producing one or more heterologous protein(s) in a bacterial host cell as defined in claim 1 required that substantial amounts of proteins be produced, in the method described in the further document (32) only minute amounts of Met-prochymosin were produced, the levels of expression being so low as to be detectable not on polyacrylamide gels but only just by Western blot analysis (see page 3359). Therefore, also document (32) was not relevant for the issue of novelty.

Admissibility of the auxiliary requests into the proceedings

The auxiliary requests had been filed in order to overcome the novelty objection raised against the main request in the decision of the opposition division. Claim 1 of the main request had been respectively amended by combining it with claim 9 of the main request (see first auxiliary request), with claim 4 of the main request (see second auxiliary request) and with both claims 4 and 9 of the main request (see third auxiliary request). These auxiliary requests could not have been filed at the oral proceedings before the opposition division. Indeed, in view of the official communication sent by the opposition division with its summons to oral proceedings, the appellant had come to said oral proceedings in the belief that novelty would be acknowledged. The announcement by the opposition division at said oral proceedings that contrary to its preliminary opinion it considered that claim 1 lacked novelty over document (22) and the invitation to file auxiliary requests just before the opposition division retired to deliberate, as it appeared from point 23 of

the minutes of the oral proceedings, had taken the appellant by surprise. The appellant was not in a position at these oral proceedings to file auxiliary requests to deal with this finding of lack of novelty over document (22) as it had prepared only to reply to certain inventive step objections. By filing the present auxiliary requests only at the stage of the appeal the appellant had not committed any procedural abuse. The auxiliary requests should therefore be allowed into the proceedings.

Novelty of the first auxiliary request

Claim 1 of the first auxiliary request corresponded to claim 9 of the main request. It differed from claim 1 of the main request in that it contained the additional technical feature that the heterologous DNA sequence(s) were fused to a DNA sequence encoding a secretion sequence. That feature was not described in either of documents (22) and (32). Therefore, the subject-matter of claim 1 of the first auxiliary request was new.

Exercise of discretion by the board on the issue of remittal of the case to the first instance

As the appellant had not committed any procedural abuse by filing its auxiliary requests at the appeal stage and as it had a right to have its requests examined by two instances, insofar as inventive step and sufficiency of disclosure were concerned, on which the opposition division had not yet decided, the case should be remitted to the first instance for further prosecution.

XIV. The respondents arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Main request - Novelty of claim 1

Claim 1 lacked novelty over document (22) as this disclosed use of a medium copy number vector in the absence of antibiotic selection. There was no reason for the skilled person not to take the disclosure made in document (22) at face value, namely that the absence of antibiotics in the otherwise detailed list of components of the medium indeed meant that no antibiotics were used. This was consistent with the skilled person's background knowledge that the vector pBGH1 was stable and did not require antibiotic selection during fermentation.

A defined medium was used in the method of document (22). Its composition was precisely detailed. Therefore, document (22) certainly did not disclose that an antibiotic was present during fermentation. Because plasmid pBGH1 encoded resistance to two antibiotics, namely ampicillin and tetracycline, it would have been necessary, if the medium were to contain an antibiotic, to indicate which antibiotic(s) was(were) present and what amount thereof had to be used. The skilled person would have realised that the fermentation conditions used in document (22) did not require the presence of an antibiotic because he/she would have easily recognised that the growth phase during fermentation took place over only 10 generations, as could be inferred from the disclosure, ie a period of time in which no loss of plasmid would have been expected. The skilled person would have known

that plasmid pBGH1, being a pBR322 derived expression construct as mentioned in document (23) (on page 257, abstract) was stable for the length of the growth period in the absence of antibiotics.

From document (23) the skilled person would have known that pBGH1 was present in the range of 30 to 35 copies per cell, ie a copy number which was encompassed by the preferred range indicated in the patent (on page 5, line 7). The copy number determination of document (23) would also be taken as indicating the copy number for the process of document (22). Even if the copy number changed from the value of document (23) it would still be close to this and so a "medium copy number" in the sense of the claim.

Claim 1 lacked novelty also over document (32). The authors of document (32) were trying to do what the inventors did and prepared plasmid pCT66 which had the features of the expression vector referred to in claim 1. Using said plasmid Met-prochymosin was expressed in *Escherichia coli* at levels which were detectable by Western blot analysis, ie the same detection method as used in the patent.

Admissibility of the auxiliary requests into the proceedings

At the oral proceedings before the opposition division, the appellant had been informed by the opposition division, before it retired to deliberate on the novelty issue, that the introduction of a dependent claim into granted claim 1 might restore novelty. This was a clear invitation to immediately file auxiliary

requests such as the present ones. By not already filing its auxiliary requests at the oral proceedings before the opposition division, the appellant committed a procedural abuse by ensuring long procedural delays at the appeal. Case T 796/02 of 1 April 2004 provided a precedent for this if all issues were to be discussed before two instances. Therefore, the auxiliary requests should not be allowed into the proceedings.

Novelty of the first auxiliary request

Novelty of the first auxiliary request was not in dispute.

Exercise of discretion by the board on the issue of remittal of the case to the first instance

If the auxiliary requests were to be allowed into the proceedings, the appellant should be treated as having foregone the opportunity to have such claims examined by the first instance and it would be appropriate, therefore, for the board not to remit the case to the first instance for further prosecution but to continue with the examination of these claim requests in full by the board only. Cases T 91/98 of 29 May 2001 and T 455/96 of 16 July 2002 were relied on as precedents.

XV. The appellant requested that the decision under appeal be set aside, that the board of appeal hold that the claims as granted are novel and that the case be remitted to the opposition division for further prosecution or, in the alternative, that the decision under appeal be set aside and that the claims of one of the first to third auxiliary requests filed on

6 December 2001 are novel and the case be remitted to the opposition division for further prosecution.

XVI. The respondents (opponents) requested that the appeal be dismissed, and that there be no remittal to the first instance.

Reasons for the Decision

Main request

Novelty (Claim 1)

1. Novelty of the subject-matter of claim 1 is denied by the respondents over either of documents (22) and (32).

2. Claim 1 is directed to a method for producing one or more heterologous protein(s) in a bacterial host cell comprising culturing in a defined medium **in the absence of antibiotic selection** a bacterial host cell transformed with one or more expression vector(s) comprising one or more heterologous DNA sequence(s) under the control of at least one regulatable promoter, an origin of replication **maintaining medium vector copy number** and a transcriptional terminator.

3. There is no definition in the patent of **a medium vector copy number**, the only information relating to this being given on page 5, lines 7 and 8 in the form of a statement of a preferred range of values (6 to 50), a preferred sub-range (10 to 20) and a discrete most preferred value (15). Nor does the experimental part of the description give any method of measuring the copy

number of the illustrated expression vectors used to produce antibodies or fragments thereof.

4. In the absence of precise information in the patent on the meaning of "medium vector copy number" or even of how or under what growth conditions to measure this, the claims can only be interpreted broadly to cover anything which reasonably might be considered as having medium copy number, when answering the question whether a method as defined in claim 1 is described in document (22) or document (32).

Vis-à-vis document (22)

5. Document (22) deals with the problem posed by the undesirable incorporation of norleucine into proteins produced in E. coli.

6. In passing (see page 533, right-hand column), production of methionyl bovine somatotropin (MBS) using a phototrophic strain of *E. coli,* W3110G, harbouring the plasmid pBGH1, is described. Fermentations were conducted in a defined medium, the composition of which is detailed in the last paragraph of page 532 without any antibiotic being mentioned. Plasmid pBGH1 is succinctly described, the indication being given that it encodes resistance to ampicillin and tetracycline (see page 532, left-hand column, Chapter entitled "*Bacteria, Phage and Plasmids*") and that it carries the bovine somatotropin structural gene under control of the E. coli tryptophan promoter (see page 533, right-hand column, first sentence of the Chapter entitled "*Production of Bovine Somatropine*"). By definition, being a plasmid, pBGH-1 has an origin of replication.

According to document (23), cited in document (22) (see reference to Calcott et al. at the end of the afore-mentioned sentence) which describes in detail the plasmid, it further contains a transcriptional terminator (see page 259, right-hand column, lines 9 to 12).

7. Thus, the skilled person reading document (22) would conclude that it incidentally describes a method for producing a heterologous protein (MBS) in a bacterial host cell (*E.coli* strain W 3110G) transformed with an expression vector (plasmid pBGH1) having a sequence encoding said protein placed under the control of a regulatable promoter (the *E. coli* tryptophan promoter), an origin of replication and a transcriptional terminator, said bacterial host cell being cultured in a defined medium.

8. Although the precise copy number per cell of plasmid pBGH1 was not mentioned in document (22), the skilled person, aware of the fact that the copy number of an expression vector is largely controlled by the origin of replication, would have taken the copy number of 30 to 35 reported in document (23) as a reliable indication and, on this basis, would have reasonably considered that plasmid pBGH1 was present in the bacterial host cell of document (22) at a medium copy number.

9. Assessment vis-à-vis document (22) further only requires consideration of whether the skilled reader would take it as implicit that the fermentation medium referred to therein actually contained an antibiotic.

10. Because plasmid pBGH1 encodes two antibiotic resistance genes (see point 6, supra), if there would have been a need for antibiotic selection, the skilled reader would have expected that precise guidance be given in the document indicating which antibiotic(s) (one of them only or both) and what amount thereof should be used. The absence of any data in this respect must lead the skilled reader to the conclusion that the fermentation medium of document (22) did not contain any antibiotic. This conclusion is further supported by the fact that the skilled reader would have recognized from the data given in the Chapter entitled "*Fermentation Methods*" on pages 532 and 533 that the growth phase during fermentation comprises only a few generations in which no significant loss of plasmid would have been expected, a finding which is not contested by the appellant. This fact means that there was no need for antibiotic selection, ie no need to introduce an antibiotic in the fermentation medium.

11. In view of the above remarks, the board concludes that claim 1 lacks novelty over document (22).

Vis-à-vis document (32)

12. Document (32) reports on an investigation of the instability of plasmids directing the expression of Met-prochymosin in *Escherichia coli* with, as in the patent, the underlying purpose of avoiding the need for antibiotic selection (see last sentence of the abstract on page 3355).

13. One of the plasmids tested was pCT66 which contained the gene coding for Met-prochymosyn, the *trp* regulatable promoter, the T7 transcriptional terminator (see Figure 1 page 3357 and 3359) and by definition an origin of replication. *E. coli* HB 101 cells were transformed with said plasmid, the plasmid being present in the bacterial host at intermediate copy numbers of approximately 40 to 60 per chromosome, and cultured in a defined medium in the absence of antibiotics (see Chapter "Methods" on pages 3356 and 3357). Samples were removed from the fermenters and analysed by Western blotting. Said analysis showed that Met-prochymosin was expressed (see Figure 4, tracks 4 to 6, on page 3359).

14. Thus, document (32) describes a method for producing, in a bacterial host cell (*E.coli* HB 101 strain) which is cultured in a defined medium that does not contain any antibiotic, a heterologous protein (Met-prochymosin), said cell being transformed with an expression vector (plasmid pCT66) having a sequence encoding said protein placed under the control of a regulatable promoter (the *E. coli* tryptophan promoter), an origin of replication and a transcriptional terminator (T7 terminator) and being present in the host cell at a copy number which may be reasonably considered as a medium copy number. This is a method which is encompassed within the scope of claim 1.

15. The argument is made by the appellant that, as only minute amounts of Met-prochymosin were produced, the afore-mentioned method of document (32) had no utility for an industrial production and, therefore, was not a method as defined in claim 1. As claim 1 does not

contain any indication as to the amount of heterologous protein to be produced, the argument is not acceptable.

16. In view of the above remarks, the board concludes that claim 1 covers subject-matter (see point 2, supra) which lacks novelty over document (32).

Conclusion

17. As claim 1 is not novel, the main request is not allowable under Article 54 EPC.

Admissibility of the first auxiliary request into the proceedings

18. It has not been disputed by the respondents that claim 1 of the first auxiliary request meets the requirements of Articles 123(2), 123(3) and 54 EPC, it being fairly based on the original application, of more restricted scope that claim 1 as granted, and novel over documents (22) and (32), the only documents relied on as destroying the novelty of claim 1 of the main request. Claim 1 of the first auxiliary request being a combination of claims 1 and 9 as granted, an Article 84 EPC objection would not be open against it, and no such objection has been made.

19. The only basis on which the respondents thus object to admission of this auxiliary request into the proceedings is that the appellant having been invited to file one or more auxiliary requests by the opposition division at the oral proceedings before it, but choosing not to do so, the board would condone an abuse of procedure by allowing the appellant to file an

auxiliary request on appeal, as remittal of this to the first instance pursuant to the appellant's request would greatly delay any final decision being reached.

20. The board agrees that exercising its discretion to admit an auxiliary request on appeal is not in conformity with the main purpose of appeal proceedings stated in Enlarged Board of Appeal decision G 9/91 (OJ EPO 1993, 408, point 18) "to give the losing party the possibility of challenging the decision of the opposition division on its merits." This the board has already done by considering and refusing the main request on appeal. By allowing into the proceedings an auxiliary request the board is faced with the choice of either considering this request as only instance or remitting it to the opposition division for further prosecution with an inevitable delay, probably of some years, before any final decision is reached.

21. The board does indeed consider the appellant's failure to file auxiliary requests when invited to do so at the oral proceedings before the opposition division, and then introducing these on appeal as amounting to a procedural abuse. The board does not accept the appellant's argument that it could not be expected to file auxiliary requests at the oral proceedings before the opposition division. The objection that claim 1 as granted lacked novelty over document (22), on which ground the appellant has lost before the opposition division and this board, had been raised in writing at the opposition stage. That the opposition division in its preliminary, non-binding opinion had indicated that it did not agree with the objection, and then at the oral proceedings indicated that it had changed its mind

is irrelevant, and something a patentee must be prepared for: the important point is that the objection based on this document had been raised by an opponent and the appellant should have been prepared to counter it by arguments or avoid it by an auxiliary request if its arguments did not succeed.

22. The appellant's argument that it is entitled to have its requests considered by two instances is not in accordance with the European Patent Convention. Article 111(1) EPC makes clear that the boards have a discretion whether to consider an issue themselves, or whether to remit it for further prosecution to the first instance. If every issue had to be considered by two instances, this would be a very strong argument for not allowing into the proceedings on appeal, requests not already in substance considered by the opposition division.

23. The strongest argument in favour of the board allowing the first auxiliary request into the proceedings is the past practice of the boards of appeal, under which such a request which avoided the grounds of appeal was invariably allowed into the proceedings. Decision T 796/02 (supra) concerned a different situation, namely the opposition division refusing to allow into the proceedings a broader claim than the one on which a first board of appeal had remitted a case. Whether the past practice should guide the boards of appeal also in future under the Rules of Procedure of the Boards of Appeal in force since 1 May 2003 is questionable. The purpose of the changes in these rules is to streamline and speed up the procedure: the purpose is not to deprive the parties of any rights. This double purpose

can however only be achieved if the parties present their case in full already during the first instance proceedings, and the opposition division is put in a position to decide all issues, including those of sufficiency of disclosure and inventive step. But the present appeal was filed before these new rules came into force.

24. Given the practice of the boards of appeal, and the fact that in this case the respondents' arguments for not allowing the first auxiliary request into the proceedings at all were only put forward at the oral proceedings, whereas in writing respondent I had asked only that the board consider all issues itself without remittal, whereas respondent II had asked for the case to be remitted to the first instance, the board decides to exercise its discretion in favour of admission of the first auxiliary request into the proceedings.

25. On the question of whether the board should exercise its discretion to itself consider all issues, or to remit the case to the first instance, there have been occasions such as occurred in decisions T 91/98 (supra) or T 455/96 (supra) where the board has itself considered a new case as only instance, though these are exceptional and in circumstances where the patents had less time to run than here, and the patentee and at least the majority of the parties were in favour of this course. In the present case the board considers as decisive for exercising its discretion in favour of remittal, the fact that the issues of both inventive step and sufficiency of disclosure have yet to be decided, and that by not remitting, the board and the respondents would be deprived of having a first

instance decision serving to focus the arguments on appeal. Article 104 EPC provides a remedy if it should turn out that there has been an unnecessary number of oral proceedings due to the conduct of one of the parties.

26. Whether any other auxiliary requests are allowed into the proceedings is not a matter which this board proposes to decide.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance for further prosecution on the basis of the first auxiliary request filed on 6 December 2001.

The Registrar: The Chairman:

W. Wolinski L. Galligani