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Datasheet for the decision of 29 January 2019

Case Number: T 1524/16 - 3.3.04

Application Number: 03719861.1

Publication Number: 1495055

IPC: C07K16/00, C07K16/46, C12N15/63, C12N15/64, C12N15/80, C12N1/15, A61K39/395

Language of the proceedings: EN

Title of invention:
Production of functional antibodies in filamentous fungi

Patent Proprietor:
Genencor International, Inc.

Opponents:
Novartis AG
Glykos Finland Oy (withdrawn)

Headword:
Functional antibodies/GENENCOR

Relevant legal provisions:
EPC Art. 56, 84, 123(2)

Keyword:
Main request and aux. requests 3 and 6 - inventive step (no)
Aux. requests 1, 4, 5 and 7 to 10 - clarity (no)
Aux.requests 1a, 2a, 4a, 5a and 7a to 10a - added subject-matter (yes)

Decisions cited:
T 0715/03

Catchword:
-

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Case Number: T 1524/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 29 January 2019

Appellant: (Patent Proprietor)	Genencor International, Inc. 925 Page Mill Road Palo Alto, California 94304 (US)
Representative:	Mewburn Ellis LLP City Tower 40 Basinghall Street London EC2V 5DE (GB)
Respondent: (Opponent)	Novartis AG Lichtstrasse 35 4065 Basel (CH)
Representative:	Cabinet Plasseraud 66, rue de la Chaussée d'Antin 75440 Paris Cedex 09 (FR)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 2 May 2016 revoking European patent No. 1495055 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chair	G. Alt
Members:	B. Claes
	L. Bühler

Summary of Facts and Submissions

I. The appeal of the patent proprietor ("appellant") is directed against the decision of the opposition division to revoke European patent No. 1 495 055 having the title "*Production of functional antibodies in filamentous fungi*".

II. Two oppositions were filed against the patent as a whole invoking Article 100(a) EPC in combination with Articles 54 and 56 EPC, Article 100(b) EPC, and Article 100(c) EPC as grounds of opposition. One opponent withdrew its opposition during the opposition proceedings.

III. The opposition division held in the decision under appeal that, whereas the main request complied with the requirements of Articles 54, 83 and 123(2) EPC, the claimed subject-matter lacked an inventive step (Article 56 EPC). The opposition division further held that claims of a first to fifth auxiliary request lacked clarity (Article 84 EPC) and that, additionally, the subject-matter of claims 1 to 9 of the fourth auxiliary request lacked an inventive step (Article 56 EPC). A sixth and seventh auxiliary request, filed during the oral proceedings, were not admitted into the proceedings for the reason that they *prima facie* lacked clarity.

Claim 2 of the main request read:

"2. A process for producing a full-length assembled immunoglobulin molecule in a host filamentous fungus, comprising the steps of:

(a) transforming said host with a first expression vector containing a fusion nucleic acid encoding

a fusion polypeptide comprising, from a 5' end of said fusion nucleic acid, first, second, third and fourth nucleic acids, wherein said first nucleic acid encodes a signal polypeptide functional as a secretory sequence in a first filamentous fungus, said second nucleic acid encodes a secreted polypeptide or functional portion thereof normally secreted from said first or a second filamentous fungus, said third nucleic acid encodes a cleavable linker and said fourth nucleic acid encodes a full-length immunoglobulin light chain;

(b) transforming said host with a second expression vector containing a fusion nucleic acid encoding a fusion polypeptide comprising, from a 5' end of said fusion nucleic acid, first, second, third and fourth nucleic acids, wherein said first nucleic acid encodes a signal polypeptide functional as a secretory sequence in a first filamentous fungus, said second nucleic acid encodes a secreted polypeptide or functional portion thereof normally secreted from said first or a second filamentous fungus, said third nucleic acid encodes a cleavable linker and said fourth nucleic acid encodes a full-length immunoglobulin heavy chain;

(c) growing said host under conditions which permit expression of said fusion DNA sequences to cause the expression of the desired polypeptides encoded by said fusion DNA sequences; and

(d) isolating said full-length assembled immunoglobulin molecule."

Claim 1 of the first auxiliary request was identical to claim 2 of the main request but for the replacement of the last part of the claim by the wording

" (d) isolating said full-length assembled immunoglobulin molecule,
wherein the immunoglobulin is secreted and wherein said process achieves levels of expression and secretion of greater than 0.5g/l of said immunoglobulin."

Claim 2 of the second auxiliary request was identical to claim 1 of the main request but for the replacement of the word "host" in the preamble and in parts (a) and (b) of the claim with the wording "Trichoderma or Aspergillus host".

Claim 1 of the third auxiliary request was identical to claim 2 of the main request but for the inclusion of the combination of the amendments contained in claim 1 of the first and second auxiliary requests.

Claim 1 of the fourth auxiliary request was identical to claim 2 of the main request but for the replacement of the word "host" in the preamble of the claim and in parts (a) and (b) of the claim with the wording "Aspergillus host".

Claim 2 of the fifth auxiliary request was identical to claim 2 of the main request but for the inclusion of a combination of the amendments contained in claim 1 of the first auxiliary request and claim 2 of the fourth auxiliary requests.

IV. With the statement of grounds of appeal, the appellant re-submitted the main request and the first auxiliary request (see section III) and submitted claims of new second to tenth auxiliary requests. It further submitted arguments to the effect that the decision under appeal should be set aside. In particular, these

were arguments in favour of inventive step and clarity. In an annex, the appellant re-submitted parts of earlier submissions before the opposition division.

Claim 1 of the second auxiliary request was identical to claim 1 of the first auxiliary request (and the same request pending before the opposition division; see section III).

Claim 1 of the third auxiliary request was identical to claim 2 of the second auxiliary request pending before the opposition division (see section III).

Claim 1 of the fourth and fifth auxiliary requests was identical to claim 1 of the third auxiliary request pending before by the opposition division (see section III).

Claim 1 of the sixth auxiliary request was identical to claim 2 of the fourth auxiliary request pending before by the opposition division (see section III).

Claim 1 of the seventh and eighth auxiliary requests was identical to claim 1 of the fifth auxiliary request pending before by the opposition division (see section III).

Claim 1 of the ninth and tenth auxiliary request were identical to claim 1 of the sixth and seventh auxiliary requests which had been submitted during the oral proceedings before the opposition division (see section III).

Claim 1 of the ninth auxiliary request read:

"1. A process for producing a full-length assembled immunoglobulin molecule in a Trichoderma or Aspergillus niger var. Awamori, Aspergillus niger or Aspergillus oryzae host filamentous fungus, comprising the steps of:

(a) transforming said Trichoderma or Aspergillus host with a first expression vector containing a fusion nucleic acid encoding a fusion polypeptide comprising, from a 5' end of said fusion nucleic acid, first, second, third and fourth nucleic acids, wherein said first nucleic acid encodes a signal polypeptide functional as a secretory sequence in a first filamentous fungus, said second nucleic acid encodes a secreted polypeptide or functional portion thereof wherein said secreted polypeptide is selected from a glucoamylase, a-amylase and aspartyl protease from Aspergillus niger var. awamori, Aspergillus niger, and Aspergillus oryzae, cellobiohydrolase I, cellobiohydrolase II, endoglucanase I and endoglucanase III from Trichoderma, and wherein said secreted polypeptide is naturally secreted by the filamentous fungal expression host, said third nucleic acid encodes a cleavable linker and said fourth nucleic acid encodes a full-length immunoglobulin light chain;

(b) transforming said Trichoderma or Aspergillus host with a second expression vector containing a fusion nucleic acid encoding a fusion polypeptide comprising, from a 5' end of said fusion nucleic acid, first, second, third and fourth nucleic acids, wherein said first nucleic acid encodes a signal polypeptide functional as a secretory sequence in a first filamentous fungus, said

second nucleic acid encodes a secreted polypeptide or functional portion thereof wherein said secreted polypeptide is selected from a glucoamylase, a-amylase and aspartyl protease from Aspergillus niger var. awamori, Aspergillus niger, and Aspergillus oryzae, cellobiohydrolase I, cellobiohydrolase II, endoglucanase I and endoglucanase III from Trichoderma, and wherein said secreted polypeptide is naturally secreted by the filamentous fungal expression host, said third nucleic acid encodes a cleavable linker and said fourth nucleic acid encodes a full-length immunoglobulin heavy chain;

(c) growing said host under conditions which permit expression of said fusion DNA sequences to cause the expression of the desired polypeptides encoded by said fusion DNA sequences; and

(d) isolating said full-length assembled immunoglobulin molecule,

wherein the immunoglobulin is secreted and wherein said process achieves levels of expression and secretion of greater than 0.5g/l of said immunoglobulin." (emphasis added by the board)

Claim 1 of the tenth auxiliary request corresponded to claim 1 of the ninth auxiliary request but for the deletion of all features relating to *Trichoderma*.

V. In a communication in preparation for the oral proceedings, the board expressed certain aspects of its preliminary opinion on the appeal. It held that the subject-matter of, *inter alia*, claim 2 of the main request and claim 1 of the third auxiliary request lacked an inventive step (Article 56 EPC). It further expressed the view that, *inter alia*, the feature "*wherein said process achieves levels of expression and*

secretion of greater than 0.5g/l of said immunoglobulin" in claim 1 of the first, second, fourth, fifth and eighth to tenth auxiliary request lacked clarity (Article 84 EPC).

VI. With a letter dated 21 December 2018, the appellant submitted claims of a **new 1st, new fourth and new seventh auxiliary request**, whereby claim 1 of these requests was identical to claim 1 of the corresponding requests filed with the statement of grounds of appeal (see section IV). Additional **auxiliary requests 1a, 2a, 4a, 5a and 7a to 10a** were submitted. Claim 1 of these requests corresponded to claim 1 of the 1st, second, new fourth, fifth, new seventh and eighth to tenth auxiliary request, respectively, in which the wording "wherein said process achieves levels of expression and secretion of greater than 0.5g/l of said immunoglobulin" was amended to read "wherein said process achieves levels of expression and secretion of said immunoglobulin greater than 0.5g/l of culture supernatant".

VII. Oral proceedings took place in the presence of the appellant. Nobody was present on behalf of the (sole) opponent ("respondent"), who had a day earlier informed the registrar of the board that it would not be attending. At the end of the oral proceedings, the chair announced the decision of the board.

VIII. The following documents are referred to in this decision:

D2: Nyyssonen *et al.* (1995), Can.J.Bot., Vol. 72, Suppl. 1, pages S885 to S890.

D3: Keränen *et al.* (1995), Current Opinion in

Biotechnology, Vol. 6, No. 6, pages 5534 to 537.

D5: Gauka *et al.* (1997), Applied Microbiology and Biotechnology (Springer, DE), Vol. 47, No 1, pages 1 to 11.

D8: WO 00/23579

D11: Final Progress Report "Develop systems for manufacturing 10,000,000 doses of emergency pharmaceutical (e.g. vaccine or monoclonal antibody) within 2 months of product identification.

D16: Maras *et al.* (1999), Glycoconjugate Journal, Vol. 16, No. 2, pages 99 to 107.

IX. The appellant's arguments can be summarised as follows:

Main request - claim 2 - inventive step (Article 56 EPC)

The claim related to the production of full-length antibodies in filamentous fungi by expressing both the light and heavy chain as a fusion to a normally secreted polypeptide or functional portion thereof.

Document D2 related to the expression of Fabs whereas document D8 related to, like the claimed invention, the production of full-length antibodies. Thus, rather than document D2, the closest prior art for the purpose of the assessment of inventive step was represented by the disclosure in document D8.

Document D2 disclosed experimental results on the expression of Fabs whereby the heavy Fd chain of the

Fab, and not the light chain, was fused to cellobiohydrolase I (CBHI), a normally secreted protein. Besides these concrete experiments, document D2 referred to two future lines of investigation (see page S889, right-hand column, second full paragraph). A first line was the production of Fabs whereby both the heavy and light chains were expressed being fused to CBHI ("*The antibody work presented here suggests that both chains should be produced as CBHI fusions to obtain most efficient expression*"; page S889, right-hand column, lines 47 to 49) and a second line was the production of complete (full-length) antibodies (see page S889, right-hand column, 52 to 54). However, both these lines of enquiry constituted uncertain speculations and, in fact, had to be combined with each other to arrive at the claimed invention.

The suggestion of the first speculative line of investigation was based on the observation that whereas upon expression of Fabs (whereby only the heavy Fd chain was fused to CBHI) all expressed light chains were detected being assembled with heavy Fd chains, the culture supernatant revealed significant amounts of cleavage products of heavy Fd chain CBHI fusions. This could be explained in that the heavy Fd chain CBHI fusion was produced at a much higher level than the light chain and that thus the latter could be limiting the yield. Hence, the suggestion to fuse both Fab chains to CBHI for expression of Fabs (see page S888, left-hand column, last full paragraph). However, the observation of the cleavage products of heavy Fd chain CBHI fusions could equally be explained by other mechanisms such as premature cleavage of CBHI from the heavy chain or poor folding of the heavy chain (leading to degradation and inherently poor assembly of the Fab). The proposal to fuse both chains of a Fab to CBH1

was therefore one of uncertain benefit. Also, the reference to "*preliminary results*" of the experiments expressing Fabs having both chains fused to CBHI (see page S889, right-hand column, 49 to 52) had to be read in this context.

The second suggested line of investigation was also speculative. In fact, document D2 did not teach the testing of full-length antibodies with both light and heavy chains fused to CBHI. It merely stated that "*Experiments are being carried out to test the capacity of Trichoderma to produce $(Fab)_2$ molecules and complete antibodies*" (page S889, right-hand column, lines 52 to 54). In the absence of any indication on whether it was actually possible to produce full-length antibodies in *Trichoderma*, the document did not teach any "solution" to producing such antibodies in filamentous fungi.

If document D2 was held to represent the closest prior art, only the disclosure of the actual experimental production of Fab antibody fragments (whereby only the heavy Fc chain was fused to CBHI) constituted an appropriate starting point for the assessment of inventive step. Speculative statements that experiments were being carried out to e.g. produce complete antibodies in *Trichoderma* could not provide such a starting point (see decision T 715/03).

The technical problem based on the technical effects achieved by the invention over the disclosure in document D2 was thus not the technical implementation of a complete antibody experiment described as being carried out in document D2 but rather the provision of an effective way to express and secrete a full-length antibody.

The claimed solution was to produce both chains of full-length antibodies as fusions and express the constructs in filamentous fungi, and the patent demonstrated that production of the antibody could be achieved in commercially relevant amounts using the methods as claimed. Thus, achieving a commercially relevant yield should also be part of the problem to be solved even if a yield is not specified in the claims.

The skilled person would have had no reasonable expectation of success of producing full-length antibodies as fusions according to the method of the claim in view of a number of concerns. These included aspects of steric hindrance; the fact that full-length antibodies were complex and big molecules; the lack of knowledge of the secretory system in filamentous fungi; the danger of incorrect folding in view of, e.g. additional disulphide bonds in the hinge region; the overall view in the art that production of full-length antibodies in yeast was generally not successful; the danger of accumulation of unfolded or misfolded proteins leading to a stress reaction in a cell; the danger of insufficient glycosylation; etc.

Besides a significant difference in size, Fabs and full-length antibodies differed in kind, including the latter having additional domains, a tetrameric rather than a dimeric structure, two additional intermolecular bonds between the heavy chains and glycan moieties in the CH2 domain which were absent in Fabs. Also, unlike Fabs, full-length antibodies could be clipped by proteases at the hinge region resulting in Fabs and because filamentous fungi were not natural expressers of antibodies, the skilled person would have considered such clipping of expressed heavy chains a true risk

having as a consequence that Fabs would be the largest antibody fragment obtainable at all in these fungi.

There was no evidence available that the authors of document D2 had been successful in expressing full-length antibodies. On the contrary, document D21 disclosed failure to obtain the hTNF-α trimer, i.e. a moderately complex oligomeric molecule falling a long way short of the complexity of a full-length antibody.

Also, post-published document D12 only endorsed the Fab fragment fusion work disclosed in document D2. It was silent on the two speculative future areas of investigation suggested in D2.

Documents D8 and D18 disclosed that full-length antibody production methods available in the yeast *Pichia pastoris* resulted in very low levels of assembled antibody unsatisfactory to be of commercial relevance.

The fact that document D2 stated that experiments for producing complete antibodies were "being carried out" would also not have provided the skilled person with a reasonable expectation of success. In fact, in document D3, a scientific review publication, two of the authors of D2 merely stated that they were "*also exploring the possibility of producing $(Fab)_2$ molecules and complete antibodies in Trichoderma*" (emphasis added by the board) and added that: "*It remains to be seen whether filamentous fungi, being eukaryotes, will be able to produce more complex, even full length, antibody molecules with multiple intermolecule disulphide bridges*" (see page 536, right-hand column, first full paragraph). Thus, two authors of document D2 themselves expressed uncertainty over the possibility

of expressing full-length antibodies in filamentous fungi for reasons of their molecular complexity. Furthermore, document D3 referred to the antibody fragments produced in document D2 as the "*first multichain molecules produced in filamentous fungi*" (see page 536, at the start of the first full paragraph).

Accordingly, the claimed subject-matter complied with the requirements of Article 56 EPC.

1st auxiliary request - claim 1 - clarity (Article 84 EPC)

The unit "g/l" in the context of the parameter referred to in the feature "levels of expression and secretion of greater than 0.5g/l of said immunoglobulin" was commonly used and accepted in the art in the context of protein production in filamentous fungi (see document D3, page 534, left-hand column, lines 15 to 17 (reference to "culture medium"); document D5, page 2, left-hand column, lines 13 to 19 (reference to "culture medium"), and Table 1; document D16, page 20, multiple references, and Table 1).

The standard understanding of the skilled person of this parameter would have been that the physical entity relating to the volume was the *culture supernatant*. Also, the application as filed (e.g. the passages on page 34, lines 16 and 17, and page 41, lines 31 to 34) and the patent reflected the understanding of the skilled person that the unit used in the claim had this standard meaning in the art.

The g/l values measured by ELISA "in shake flask cultures" in the application as filed (e.g. on page 34,

lines 16 to 17), and in the patent, were measured in the *culture supernatant,* and the physical entity referred to by volume was thus this liquid.

Auxiliary request 1a - claim 1 - added subject-matter (Article 123(2) EPC)

The claim now referred to the parameter being 0.5g/l of the culture supernatant and the application as filed provided a basis for this amendment, *inter alia*, on page 34, lines 16 to 17, on page 41, lines 8 to 9, on page 20, lines 7 to 15, and in the methodology as described in the remainder of the examples (e.g. page 41, lines 28 to 37).

The amendment furthermore merely stated the standard meaning in the art of the unit used to characterise the parameter. The terms "culture medium" and "culture supernatant" meant and were equal to the liquid component of the culture (see documents D3 and D5 and e.g. the passages on page 34, lines 16 and 17, and page 41, lines 31 to 34, of the application as filed).

Second, new fourth, fifth, new seventh and eight to tenth auxiliary request
claim 1 - clarity (Article 84 EPC)

No further arguments were submitted by the appellant.

Auxiliary requests 2a, 4a, 5a and 7a to 10a
claim 1 - added subject-matter (Article 123(2) EPC)

No further arguments were submitted by the appellant.

Third auxiliary request - claim 1 - inventive step (Article 56 EPC)

Trichoderma and *Aspergillus* were hosts in which commercially useful high levels of expression could be obtained. The skilled person had no reasonable expectation of success that these species could provide such levels.

Sixth auxiliary request - claim 1 - inventive step (Article 56 EPC)

No further arguments were submitted by the appellant.

X. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of the main request filed with the statement of grounds of appeal, or, alternatively, on the basis of the claims of one of the following claim sets in the indicated order:

- 1st auxiliary request and auxiliary request 1a filed with letter dated 21 December 2018;
- second auxiliary request filed with the statement of grounds of appeal;
- auxiliary request 2a filed with letter dated 21 December 2018;
- third auxiliary request filed with the statement of grounds of appeal;
- new fourth auxiliary request and auxiliary request 4a filed with letter dated 21 December 2018;
- fifth auxiliary request filed with the statement of grounds of appeal;
- auxiliary request 5a filed with letter dated 21 December 2018;
- sixth auxiliary request filed with the statement of

grounds of appeal;
- new seventh auxiliary requests and auxiliary request 7a filed with letter dated 21 December 2018;
- eighth auxiliary request filed with the statement of grounds of appeal;
- auxiliary request 8a filed with letter dated 21 December 2018;
- ninth auxiliary request filed with the statement of grounds of appeal;
- auxiliary request 9a filed with letter dated 21 December 2018;
- tenth auxiliary request filed with the statement of grounds of appeal;
- auxiliary request 10a filed with letter dated 21 December 2018.

XI. The respondent has made no submissions in the appeal proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. The duly summoned respondent was not present nor represented during the oral proceedings as announced to the registrar of the board. In accordance with Rule 115(2) EPC and Article 15(3) RPBA, the board decided to continue the proceedings in the respondent's absence.

Main request - claim 2 - inventive step (Article 56 EPC)

3. Claimed is a very generally defined process for producing full-length assembled antibodies in

filamentous fungi by expressing both the light and heavy chain as a fusion to a normally secreted polypeptide or functional portion thereof.

Closest prior art

4. The opposition division held the disclosure of document D2 to represent the closest prior art for the purpose of the assessment of inventive step. In its communication in preparation of oral proceedings (see section V), the board likewise considered the disclosure in document D2 of experiments carried out to produce, *inter alia,* complete antibodies in *Trichoderma* to represent the closest prior art.

5. The relevant part of document D2 is on page S889, right-hand column, lines 34 to 54, and reads:

"Antibodies and their engineered forms have numerous applications. For applications which demand large quantities of antibodies, strategies providing cheap and high level production would be needed. ***Antibody production in Trichoderma (Nyyssonen et al. 1993) was the first example of expression of complex multichain molecules in filamentous fungi.*** *Compared with other microbial production systems the yields are very favourable especially considering that antibodies are secreted into the culture medium in an assembled and immunologically active form. Production of more complex, even full length* [sic] *antibody molecules with multiple intermolecule S—S bridges has been problematic for instance in E. coli. Thus filamentous fungi, being eukaryotes, might prove to be more suitable production hosts.* ***The antibody work presented here suggests that both chains should be produced as CBHI fusions to obtain most efficient expression.*** *Preliminary results*

indicate that it is possible to produce ***Fab molecules*** *with Trichoderma so that both the light and heavy Fd chain are produced fused to CBHI.* ***Experiments are being carried out to test the capacity of Trichoderma to produce*** *(Fab)$_2$ molecules and* ***complete antibodies***." (emphasis added by the board)

6. The appellant argued that the disclosure in document D8 was closer to the claimed subject-matter than that in document D2 because it concretely disclosed the expression of full-length antibodies, albeit in yeasts.

7. The board considers that although the disclosure in other documents cited in these proceedings (such as document D3 or D8, the latter as argued by the appellant) may possibly equally qualify as an appropriate starting point for the skilled person to arrive at the claimed subject-matter, the existence of such alternative choices cannot disqualify a negative outcome of an assessment of inventive step based on one of the alternatives, here document D2 (see further on).

8. The appellant has not argued in these proceedings that document D2 could not qualify as the closest prior art but rather that the experiments referred to by the board as representing the closest prior art were merely speculative and therefore could not have represented an appropriate starting point for the skilled person (see point 6).

9. The appellant submitted that in document D2, both announced future lines of investigation, i.e. the production of both the heavy and light chains fused to cellobiohydrolase I (CBHI) and the experiments relating to the production of full-length antibodies in *Trichoderma*, were uncertain and speculative and could

as such not provide the appropriate starting point for the assessment of inventive step. The appellant referred to decision T 715/03, of 16 January 2006. It was held in particular that the first suggestion in document D2 was based on an unproven hypothesis and thus one of uncertain benefit and that the second was purely speculative. In relation to the second speculative future line of investigation, document D2 did not teach the testing of full-length antibodies with both light and heavy chains fused to CBHI but merely stated that "*Experiments are being carried out to test the capacity of Trichoderma to produce $(Fab)_2$ molecules and complete antibodies*" (page S889, right-hand column, lines 52 to 54). In the absence of any indication whether it was actually possible to produce full-length antibodies in *Trichoderma*, the document could not teach any "solution".

10. The appellant further submitted that if document D2 represented the closest prior art, only the disclosed actual experimental production of Fab antibody fragments, whereby only the heavy Fc chain is fused to CBHI, could provide the starting point for the assessment of inventive step. Speculative statements that experiments are being carried out to e.g. produce complete antibodies in Trichoderma, as the opposition division had considered, could not provide such a starting point. The technical problem based on the technical effects achieved by the invention over the closest prior art represented by document D2 was thus not "*the technical implementation of this experiment described as being carried out in document D2*" but rather "*the provision of an effective way to express and secrete a full-length antibody*".

11. Decision T 715/03, *supra*, relates to "second medical-use" claims, i.e. to the use of a particular chemical compound in the treatment of mammals having a particular condition (here Tourette's syndrome (TS), obsessive compulsive disorder or vocal tic disorder). When deciding the case, the board held that a document disclosing a double blind pilot phase II study (clinical trail on efficacy and tolerability) of the known antipsychotic compound ziprasidone in TS patients which was unfinished and the results of which were unknown, provided no information "*about a beneficial effect in TS patients*". The board concluded that "*it would be speculative for the skilled person to pretend that document (1) teaches that ziprasidon possesses an activity useful for the treatment of* TS" and concluded that hence known therapies for TS represented the closest prior art.

12. However, the claim underlying the present decision is for a process for producing a full-length assembled immunoglobin molecule (e.g. an antibody) in a host filamentous fungus, i.e. a claim devoid of any medical use connotation. Under these circumstances, therefore, the board cannot agree with the appellant that the principles underlying decision T 715/03, *supra*, necessarily prevent the board from holding the disclosure in document D2 to represent the closest prior art.

13. Accordingly, the board is satisfied, first, that document D2 discloses, in the context of Fab production, that, to optimise expression efficiency, both chains (i.e. the light chain and Fd molecule) should be produced as CBHI fusions and second that experiments are being carried out to test the capacity

of the production of complete antibodies in *Trichoderma* (see last two sentences in the quote in point 5).

Problem to be solved

14. Based on the effect of the difference between the disclosure in document D2 of the fact that experiments were being carried out to produce complete antibodies in *Trichoderma* and the claimed subject-matter, the objective technical problem to be solved by the skilled person can be defined as the provision of a process for producing full-length assembled antibodies in *Trichoderma*.

15. The board notes that for the purpose of the formulation of the problem to be solved by the claimed subject-matter, issues of attaining an economically relevant yield of the whole antibody to be produced in *Trichoderma*, as argued by the appellant, are in fact of no relevance for the claimed process as a feature or features for such potentially advantageous effect appear(s) not to be part of the claims and have also not been argued by the appellant to be.

16. Based on the experiments disclosed in the patent in suit, the board is satisfied that the above formulated problem is indeed solved by the claimed subject-matter.

Obviousness

17. For assessing inventive step of the claimed subject-matter based on the announcement of the production of complete antibodies in *Trichoderma* as disclosed in document D2 (see above), it needs to be established whether the skilled person, when designing the experiment, would have considered expressing both the

(complete) light chain and (complete) heavy chain as fusions to a normally secreted polypeptide or functional portion thereof, such as for instance CBHI also disclosed in document D2.

18. The board notes that the appellant has not contested that document D2 itself, also in combination with the common general knowledge, would have taught the skilled person the necessary tools for implementing the experiments mentioned. The appellant has also not argued, contrary to the teaching in document D2, that to optimise expression efficiency in *Trichoderma*, both chains should be produced as CBHI fusions (see point 13 above). The appellant has rather argued that the skilled person, when contemplating the claimed constructs, would not have had a reasonable expectation that full-length antibody production would be successful when expressed in *Trichoderma*.

19. In support of the alleged lack of expectation, the appellant has enlisted several putative concerns that the skilled person might have had. These related, *inter alia*, to steric hindrance, to the fact that full-length antibodies are complex big molecules, to the lack of knowledge of the secretory system in filamentous fungi, to the danger of incorrect folding in view of e.g. additional disulphide bonds in the hinge region, to the overall view in the art that production of full-length antibodies in yeast was generally not successful, to the danger of accumulation of unfolded or misfolded proteins leading to a stress reaction in a cell, to the danger of inefficient glycosylation, etc.

20. The board is, however, of the opinion that any of these concerns, which the skilled person could have had before the publication of document D2, would have been

alleviated by the statement in document D2 that experiments of producing complete antibodies were in fact *being carried out*. Indeed, the appellant has failed to identify any statements in document D2 which can be qualified as speculative or consciously ignoring a prevailing prejudice.

21. In relation to concerns of the skilled person in the period after the publication of document D2, the board has seen no evidence of any failure in *Trichoderma*. Furthermore, in the board's view, neither possible reports of failure in other organisms would have led the skilled person to refrain from implementing the teaching of document D2 in view of the fact that extrapolating results from one organism to another in this context is not always possible. The board considers also in this context that the absence of a publication of the results of the experiments of document D2 in the interval preceding the priority date would not have stopped the skilled person as they would have understood that this could have been for reasons other than failure.

22. Accordingly, the board has seen no evidence on file demonstrating that the skilled person would have had reason to expect failure when implementing the solution as claimed. Therefore, the board is satisfied that the skilled person would have had a reasonable expectation of success to express full-length antibodies in accordance with the claimed method.

23. In view of the above considerations, the claimed subject-matter lacks an inventive step.

1st auxiliary request - claim 1 - clarity (Article 84 EPC)

24. In its communication in preparation for oral proceedings (see section V), the board had expressed the opinion that the amendment introduced in the claim, i.e. "levels of expression and secretion of greater than 0.5g/l of said immunoglobulin" (see section III) lacked the identification of the physical entity representing the volume ("l") in the recited parameter defining the concentration of the immunoglobulin ("g/l"). In fact, the board considered that the physical entity representing the volume ("l") could be e.g. the total volume of the fungal culture as a whole or the liquid compound obtainable after its physical separation from the cell mass or cell compounds by, for example, centrifugation. The feature introduced into the claims therefore lacked clarity.

25. In response, the appellant referred to a number of passages in the cited prior art documents in which, as was the case in the claim, the unit "g/l" was used without indication of the physical entity referred to by the volume unit "l" (see Table 1 in documents D5 and D16 and multiple references on page 20 of document D16) and considered that, thus, the use of the unit as contained in the claim constituted common practice in this context. It was further standard practice in the technical field that the physical entity referred to by the volume unit in the unit "g/l" of the parameter referred to in the claim was the *culture supernatant*, i.e. the liquid component of the fungal culture. In this context, the appellant referred to passages in document D3 ("*Several mutant strains are available that produce cellulase yields in the range of 40gl^{-1}* ***of culture medium.***"; see page 534, left-hand column, lines 15 to 17) and document D5 ("*Production levels of most*

non-fungal proteins, of mammalian, bacterial, avian or plant origin, are low compared to those of homologous proteins, and reach levels that, with some exceptions, do not exceed a few tens of milligrams per liter ***of culture medium.***"; see page 2, left-hand column, lines 13 to 19). Further support that it was standard in the technical field to refer to the culture supernatant in this context could also be found in the passages on page 34, lines 16 and 17, and page 41, lines 31 to 34, of the application.

26. The board accepts that the cited prior art documents in a number of cases recites the unit "g/l" without explicitly indicating the physical entity referred to by the volume unit in this unit. The consequence is, however, that these documents do not provide an insight into what would be the common understanding of the skilled person on the exact nature of the physical entity referred to by "l" in the context of the unit "g/l".

27. The board notes further that the two passages referred to by the appellant in documents D3 and D5 refer not to the fungal culture supernatant but to the **culture medium** (see point 25 above). These references can therefore also not be considered to establish that the skilled person would have unambiguously understood the volume unit "l" to refer to the supernatant.

28. The board further considers that the sentence on page 34, in lines 16 and 17, of the application as filed and in the patent, which reads *"Quantification of the light chain in* ***culture supernatants*** *was performed by enzyme-linked immunosorption assays (ELISA)"* (emphasis added by the board), the sentence on page 41 in lines 31 to 34 of the same, which reads "*After*

adding appropriately diluted ***culture supernatant,*** *incubation, and then washing the wells, the bound IgG1 from the supernatant was detected by addition of an goat anti human κ (bound and free) antibody conjugated with HRP followed by a color development reaction."* (emphasis added by the board) are also of no help to establish that the volume unit conventionally refers to the supernatant since they merely refer to experiments conducted in the context of the application without providing a clear definition of the parameter contained in the claim. This becomes all the more apparent when reading the sentences preceding those referred to by the appellant i.e. "*The strain produced approximately* ***1.5 g/l*** *of trastuzumab light chain (κ chain)* ***in shake flask culture*** *according to ELISA*" (page 34, lines 18 to 20) and "*Up to approximately* ***0.3 g/l*** *assembled IgG was measured by ELISA* ***in shake flask cultures*** *of the best transformant (1-LC/HC-3).* (page 41, lines 28 to 29)", which could be understood to directly refer to the whole culture volume rather than to the volume of the supernatant only.

29. The board notes finally that the argument of the appellant that the particular g/l values measured by ELISA "in shake flask cultures" in the application as filed and in the patent were measured in the culture supernatant and that, thus, the physical entity referred to by volume "l" in the unit "g/l" measured in the claim had to refer to the culture supernatant must fail in the absence of an understanding of which exact physical entity, i.e. culture volume or supernatant volume, is conventionally referred to.

30. In view of the above considerations, the board considers the claim to not be clear as required by Article 84 EPC.

Auxiliary request 1a - claim 1 - added subject-matter (Article 123(2) EPC)

31. The board cannot see a basis for the specific parameter "0.5 g/l of the culture supernatant" in the claim in the disclosure on page 34, lines 16 to 17, and on page 41, lines 8 to 9, of the application as filed (see point 7 above), nor in the methodology as described in the remainder of the examples in the application as filed (see for example on page 41, lines 28 to 37).

32. The board notes furthermore that also the passage referred to on page 20, lines 7 to 15, of the application as filed, which reads:

"*In one study, 100 ng/ml of light chain and 50-80 ng/ml of heavy chain were detected in the culture supernatant and approximately 50-70% of the heavy chains were associated with light chain (Horwitz, A.H. et al., 1988, Proc. Natl. Acad. Sci USA). Full-length antibody in a correctly assembled form has been produced in the yeast Pichia pastoris (WO 00/23579). However, the highest yields reported were 36 mg/l.*

In contrast, the system utilized herein has achieved levels of expression and secretion of greater than 0.5 g/l of full-length antibody. It is routinely found that greater than 1 g/l of the antibody may be recovered from the fermentation broth."

does not appear to support subject-matter characterised by this feature because it refers to the "fermentation broth" rather than to the supernatant, i.e. yet another term argued to be synonymous and having the meaning

"culture supernatant" and being referred to by "l" in the unit "g/l".

33. The claim accordingly relates to added subject-matter and therefore infringes the requirements of Article 123(2) EPC.

Second, new fourth, fifth, new seventh and eight to tenth auxiliary request - claim 1 - clarity (Article 84 EPC)

34. These claims (see section IV and V) comprise the same amendment as claim 1 of the 1st auxiliary request.

35. Accordingly, the above considerations in points 26 to 30 above apply *mutatis mutandis* to these claims.

Auxiliary requests 2a, 4a, 5a, 7a, 8a to 10a - claim 1 - added subject-matter (Article 123(2) EPC)

36. These claims (see section IV and V) comprise the same amendment as claim 1 of auxiliary request 1a.

37. Accordingly, the above considerations in points 31 to 33 that the claim relates to added subject-matter and therefore infringes the requirements of Article 123(2) EPC apply *mutatis mutandis* to these claims.

Third auxiliary request - claim 1 - inventive step (Article 56 EPC)

38. As compared to claim 2 of the main request, this claim now defines the host filamentous fungus specifically to be *Trichoderma* (or *Aspergillus*). However, the relevant disclosure in document D2, which represented the closest prior art for assessing inventive step of the subject-matter of claim 1 of the main request, is

concerned with protein production methods in *Trichoderma* (see the last sentence in the quote reproduced from document D2 in point 5 above). The assessment of inventive step in relation to claim 2 of the main request was made for the embodiment of that claim relating to *Trichoderma* (see points 14 to 22 above). Accordingly, the amendment is not suitable for altering the conclusion in relation to inventive step reached in point 23 above.

39. The appellant has submitted that *Trichoderma* and *Aspergillus* were the very host strains in which commercially relevant high levels of expression could be obtained and that the skilled person would have not reasonably expected that these species could provide such levels.

40. The board notes, however, that considerations of yield should not to be taken into account for formulating the technical problem to be solved in the present context either. Indeed, the claim does not specify any particular level of production or yield but also covers methods for producing low yields of full-length assembled immunoglobulin molecules in *Trichoderma*. Furthermore, since the use of Trichoderma is also disclosed in document D2, the document representing the closest prior art, any argument based on the very selection of this specific fungus for the process must fail.

41. In view of the above considerations, the claimed subject-matter lacks an inventive step.

Sixth auxiliary request - claim 1 - inventive step (Article 56 EPC)

42. The claim is identical to claim 2 of the fourth auxiliary request pending before by the opposition division (see sections III and IV) and corresponds to claim 1 of the third auxiliary request having the aspects referring to *Trichoderma* deleted.

43. In point 13 of the decision under appeal, the opposition division held in relation to, *inter alia*, claim 2 of the then pending fourth auxiliary request: "*Compared to the claims of the MR, the claims of the AR4 further differ from the closest prior art D2 in that the host filamentous fungus belongs to the Aspergillus genus. P has not provided further arguments in this respect.*
In absence of any evidence that filamentous fungi from the Aspergillus genus (whatever the Aspergillus strain selected) provide any particular unexpected effect over the T. reesei strain of D2, an inventive step cannot be derived from the restriction to filamentous fungi from the Aspergillus genus since it is well known in the art that both strains from the Trichoderma genus and strains from the Aspergillus genus are suitable for the production of high quantity of heterologous proteins (see for example D5: page 1, right-hand column, second paragraph). Secreted polypeptides suitable as fusion partner for the production of recombinant polypeptides in Aspergillus are also well known in the art (see document D5: Table 1).

Therefore, in view of the above comments and following mutatis mutandis the same reasoning as for the MR, claims 1 to 9 of the AR4 are considered to lack an

inventive step (Article 56 EPC)." (emphasis added by the board).

44. During the appeal proceedings, the appellant has not filed any further arguments beyond those in relation to inventive step of the subject-matter of claim 2 of the main request and claim 1 of the third auxiliary request.

45. The board, therefore, has not been presented with any reason to come to a different conclusion on inventive step for the subject-matter of this claim as for the former claims.

46. Accordingly, the board decided that the claimed subject-matter lacked an inventive step.

Conclusion

47. In summary, the board concludes that none of the claim requests in these appeal proceedings meet the requirements of the EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated