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D E C I S I O N
of 5 February 2004

Case Number: T 0100/01 - 3.3.8

Application Number: 92902109.5

Publication Number: 0564531

IPC: C12N 15/62

Language of the proceedings: EN

Title of invention:

Enrichment method for variant proteins with altered binding properties

Patentee:

GENENTECH, INC.

Opponent:

Cambridge Antibody Technology Limited

Headword:

Variant proteins/GENENTECH, INC.

Relevant legal provisions:

EPC Art. 54, 56

Keyword:

"Granted claims - novelty - yes"

"Granted claims - inventive step - yes"

"Remittal of a question to the Enlarged Board of appeal - no"

Decisions cited:

G 0009/91, G 0010/91, G 0001/95, G 0007/95, T 0182/89,
T 1066/92, T 0793/93, T 0397/02

Catchword:

-



Case Number: T 0100/01 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 5 February 2004

Appellant: Cambridge Antibody Technology Limited
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 27 November 2000
rejecting the opposition filed against European
patent No. 0564531 pursuant to Article 102(2)
EPC.

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 564 531 with the title "Enrichment method for variant proteins with altered binding properties" was granted with 27 claims on the basis of European patent application No. 92 902 109.5. Four priorities were claimed from US 621667 of 3 December 1990, US 683400 of 10 April 1991, US 715300 of 14 June 1991 and US 743614 of 8 August 1991.

Granted claims 1 and 13 read as follows:

"1. A method for selecting novel binding polypeptides comprising:

(a) constructing a replicable expression vector comprising a transcription regulatory element operably linked to a gene fusion encoding a fusion protein wherein the gene fusion comprises a first gene encoding a polypeptide, and a second gene encoding at least a portion of a phage coat protein;

(b) mutating the vector at one or more selected positions within the first gene thereby forming a family of related plasmids;

(c) transforming suitable host cells with the plasmids;

(d) infecting the transformed host cells with a helper phage having a gene encoding the phage coat protein;

(e) culturing the transformed infected host cells under conditions suitable for forming recombinant phagemid particles containing at least a portion of the plasmid and capable of transforming the host, the conditions adjusted so that the amount or number of phagemid particles displaying more than a single copy of the fusion protein on the surface of the particle is less than about 20%;

(f) contacting the phagemid particles with a target molecule so that at least a portion of the phagemid particles bind to the target molecule; and

(g) separating the phagemid particles that bind from those that do not."

"13. Phagemid particles, obtainable by

(a) constructing a replicable expression vector comprising a transcription regulatory element operably linked to a gene fusion encoding a fusion protein wherein the gene fusion comprises a first gene encoding a polypeptide, and a second gene encoding at least a portion of a phage coat protein, a DNA triplet codon encoding an mRNA suppressible terminator codon selected from UAG, UAA and UGA being inserted between the fused ends of the first and second genes, or being substituted for an amino acid encoding triplet codon adjacent to the gene fusion junction,

(b) mutating the vector at one or more selected positions within the first gene thereby forming a family of related plasmids;

(c) transforming suitable host cells with the plasmids;

(d) infecting the transformed host cells with a helper phage having a gene encoding the phage coat protein; and

(e) culturing the transformed infected host cells under conditions suitable for forming recombinant phagemid particles containing at least a portion of the plasmid and capable of transforming the host, the conditions adjusted so that the amount or number of phagemid particles displaying more than a single copy of the fusion protein on the surface of the particle is less than about 20%."

Dependent claims 2 to 12 related to further features of the method of claim 1. Dependent claims 14 to 21 related to further features of the phagemids of claim 13.

Independent claim 22 related to a method for selecting novel binding polypeptides comprising the same steps as the method of claim 1 whereby the transcription regulatory element was operably linked to DNA encoding a protein of interest containing one or more subunits. Independent claim 26 related to a method for selecting novel binding polypeptides comprising steps (a) to (f) of the method of claim 1 plus additional steps (g) and (h) whereby the transcription regulatory element was operably linked to a gene fusion which comprised a first gene encoding a polypeptide operably connected to a linking amino acid sequence, and a second gene encoding at least a portion of a phage coat protein.

- Dependent claims 23 to 25 and 27 respectively related to further features of the methods of claims 22 and 26.
- II. An opposition was filed under Article 100(a) EPC for lack of novelty of the subject-matter of claims 1, 22 and 26 for all Designated Contracting States except Monaco vis-à-vis document (1) (cf infra) and lack of inventive step of the subject-matter of claim 13. The Opposition Division rejected the opposition pursuant to Article 102(2) EPC.
- III. The Appellants (Opponents) filed an appeal and submitted a statement of grounds of appeal on 27 March 2001.
- IV. The Respondents (Patentees) answered to the grounds of appeal on 15 October 2001.
- V. On 11 September 2003, the Board sent a communication under Article 11(1) of the Rules of procedure of the Boards of Appeal, setting out the main issues to be considered as well as its preliminary, non-binding opinion.
- VI. Both parties answered to this communication. On 5 January 2004, the Appellants filed eight new documents (documents (39) to (46)) together with their answer. The Respondents objected to this filing and, in turn, filed seven new documents on 29 January 2004.
- VII. Oral proceedings took place on 5 February 2004.

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

(1): WO 92/01047, claiming five priorities, inter alia from 10 July 1990 (filing date of the first priority document) and from 12 November 1990 (filing date of the third priority document);

(2): Armstrong, N. et al., in "Phage Display of Peptides and Proteins; A laboratory Manual, Chapter 15, 1996, in particular pages 262 to 263, Eds. B.K. Kay, J. Winter and J. McCafferty, Academic Press, San Diego, Ca, USA;

(5): Chappel, J.A. et al., Journal of Immunological Methods, Vol. 221, 1998, pages 25 to 34;

(7): Bass, S. et al., PROTEINS: Structure, Function, and Genetics, Vol. 8, December 1990, pages 309 to 314;

(15): Barbas III, C.F. et al., Proc. Natl. Acad. Scie. USA, Vol. 88, September 1991, pages 7978 to 7982;

(46): US 4 673 641.

IX. The Appellants' submissions in writing and during oral proceedings insofar as they are relevant for the present decision may be summarized as follows:

Admissibility of the documents/declarations filed with the submissions dated 5 January 2004

All these documents were filed within the time limit set by the Board. None of them raised new aspects, nor did they change the framework of the appeal.

The filing of post-published documents could not be avoided since what was aimed at was to explain what was inherent in a prior art disclosure under Article 54(3)(4) EPC (ie document (1)).

The two declarations which included new experimental data could not have been filed earlier since they were in direct answer to the Board's communication.

Document (46) which related to the same field as the patent in suit, ie expression in bacteria, was very relevant to inventive step.

Novelty of the subject-matter of claim 1

- Document (1) was novelty destroying for the subject-matter of claim 1 under Article 54(3)(4) EPC as passages of said document which enjoyed an earlier priority date (12 November 1990) than the earliest priority date (3 December 1990) of the patent in suit disclosed the method of claim 1, in particular on page 48, lines 37 to 48, where steps (a) and (d) were disclosed expressis verbis. Steps (c), (f) and (g) did not need to be mentioned as they were obvious routine steps.

- On page 48 of the said document, step (b) was not disclosed *expressis verbis*. Yet, mutagenizing the gene encoding the polypeptide to be displayed once it had been inserted in the replicable expression vector was clearly disclosed in other parts of document (1), for example on page 7, lines 14 to 17 and page 10, lines 23 to 25. Admittedly, the replicable expression vector mentioned in these passages was a phage rather than a phagemid. However, the skilled person reading the patent specification as a whole would understand the mutagenesis as being equally applicable to phagemids, all the more so that the relevant passage on page 48 was part of example I which was a precursor of the other specific examples.

- The feature that the conditions should be adjusted when culturing the transformed host cells (step (e)) was also not disclosed *expressis verbis* in the passage on page 48 of document (1). Yet, there was no information in the patent in suit on how to adjust said conditions, the only relevant passage being on page 17 where the amount of immunoreactive material per phage particle was estimated to be about 10% when the cultures were grown under the specific conditions of Example IV. Thus, the feature in step (e) of claim 1 that the growth conditions should be adjusted was an unusual parameter for which the skilled person was given no teaching of how to put it into practice. In such a situation, the standard of proof mentioned in the case law as being required when novelty was attacked on the basis of the inherent disclosure of a prior art must fall from being "beyond all reasonable doubts" (eg T 793/93 of 27 September 1995) to being the usual standard of "balance of probabilities" (eg

T 182/89, OJ EPO 1991, 391). Indeed, this practice was that recommended in a similar situation in the Guidelines for Examination at the European Patent Office, Chapter C IV, point 7.5.

In the present case, there existed three lines of indirect evidence that, irrespective of the growth conditions, the number of phagemid particles displaying more than one single copy of the gene fusion on the surface of the particles was less than 20%:

- Later document (5) demonstrated that 34% and 1% of **phages** respectively displayed 1 and 4 copies of a fusion protein when the fusion involved the coat protein VIII, 2700 copies of which were present at the surface of the phage. If as taught in document (1), the fusion involved the coat protein III, about 5 copies of which were present at the surface of the phage, one would, of course, expect that the number of phages displaying more than a single copy of the fusion protein on the surface would be much less than 20%. In the same manner, document (15) taught that monovalent display would be achieved by constructing and using coat protein III fusions.

- Later document (2) showed in Figure 1 that the majority of rescued **phagemid** particles had lost the fusion protein, the reason therefore being given as the proteolytic degradation of said fusion.

- The Appellants had provided during the opposition proceedings experimental evidence reproducing the claimed method under various growth conditions, which unambiguously showed that no more

than 9% of the phagemid particles ever carried a protein III fusion. Thus, working according to the teaching of document (1), one would necessarily carry out the method of claim 1.

For these reasons, document (1) anticipated the subject-matter of claim 1.

Inventive step of claim 13

Document (7) was the closest prior art. It disclosed phagemids, the genome of which contained a gene resulting from the fusion of a first gene encoding the polypeptide of interest with a gene encoding part of a phage coat protein.

The problem to be solved could be defined as producing alternative phagemids.

The solution thereto were phagemids, the genome of which comprised a suppressible stop codon between the two fused DNAs.

The existence of suppressible stop codons was well known at the priority date. Document (46) disclosed their uses in a similar situation ie. for the production in E. coli of a protein in fused and unfused forms. This document also acknowledged the need for varying the proportions of these two types of molecules (col. 11, point 5.3).

For these reasons, the combination of the teachings of documents (7) and (46) rendered obvious the subject-matter of claim 13.

Inventive step of claim 1

Claim 1 was opposed under Article 100 a) EPC which comprised novelty and inventive step as grounds of opposition. Although the extent to which claim 1 was attacked was originally identified as lack of novelty, it remained that both grounds had always been in the proceedings. The situation was analogous to that where inventive step was initially argued against, on the basis of one document and another relevant document was cited later on. Accordingly, discussing the inventive step of the subject-matter of claim 1 was admissible.

Sufficiency of disclosure in relation to claim 1

Admittedly, lack of sufficient disclosure in relation to the subject-matter of claim 1 was a ground of opposition which was expressly raised for the first time in the grounds of appeal. The Respondents did not give their consent to the issue being discussed. Yet, they had **implicitly consented** to it when discussing the novelty issue since they repeatedly admitted that there was no direct way to quantify the number of phagemid particles displaying more than one copy of the fusion protein on the surface. It should, thus, be allowable to assess sufficiency of disclosure. If it was not, then the issue should be discussed under inventive step (see previous point). Alternatively, the case should be remitted back to the Opposition Division which, in accordance with the Enlarged Board's Opinion G 10/91 (OJ EPO 1993, 420) had the power to raise a new ground of opposition. In this context, the decision T 1066/92 of 5 July 1995 should be taken into account where an

objection of lack of sufficient disclosure had then only been raised on appeal, the patent proprietors had refused to have it considered and the competent Board had decided to remit the case to the first instance. Finally, if none of these courses of action were acceptable, it was suggested that a question be referred to the Enlarged Board of Appeal (see point XI, *infra*).

- X. The Respondents' arguments in writing and during oral proceedings insofar as they are relevant to the present decision may be summarized as follows:

Admissibility of the documents/declarations filed with the submissions dated 5 January 2004

The declarations should not be admitted in the proceedings since they raised entirely new aspects in the form of new experimental reports. The documents filed in relation to the novelty issue should also not be admitted since they were post-published by seven years or more compared to the priority date. It was sufficient to rely on document (1) alone to reach a conclusion on novelty.

Document (46) was not concerned with phagemid displays at all but with the stabilisation of a soluble protein by co-aggregation. It was irrelevant to the issue of inventive step.

Novelty of the subject-matter of claim 1

In document (1), the disclosure relative to phagemids consisted of one single paragraph on page 48, which was

written in such an obscure manner that it was open to many different interpretations.

Reference was made in the second part of this paragraph to a modified fd gene III. It was not clear that this was a disclosure of said gene being fused to the gene encoding the polypeptide of interest as required in step (a) of the claimed method.

A teaching corresponding to step (b) was missing. Reference to further passages in document (1) could not cure this deficiency because these passages dealt with phage displays rather than with phagemid displays and furthermore, it was not clear that any of them taught that the gene of interest should be mutated after being fused to the gene encoding part of the coat protein in the phage DNA.

Step (d) was also not taught on page 48 since the expression "superinfection with modified phage such as K07" might mean that K07 was modified which was clearly in contradiction with the teachings in step (d).

Step (e) referred to adjusting growth conditions and this feature was not mentioned in document (1). Contrary to the Appellants' opinion, it was not a matter of inherency that less than 20% of the phagemid particles would display more than one copy of the fusion protein. Indeed, changing conditions could significantly alter the valency of the display. This was shown on page 71 of document (1) where it was stated that by modifying the helper phage, one could get all of the coat protein III on the surface of the phage in the form of a fusion protein. It was also the

result which the Appellants had obtained in the experimental evidence they produced.

For these reasons, document (1) did not destroy the novelty of the subject-matter of claim 1, nor that of claims 22 or 26.

Inventive step of the subject-matter of claim 13

Document (7) did not suggest that the phagemids which it described could be improved upon. The fact that by introducing a suppressible stop codon between the gene of interest and the coat protein gene, one could get either monovalent display of the protein of interest on the phage surface or, **alternatively**, the protein of interest in an unfused form was certainly unexpected on the basis of its teaching and also quite advantageous.

Document (46) did not relate to the field of phagemid display. It described a DNA construct comprising a suppressible stop codon between the gene of interest and a "carrier" gene. The purpose of this construct was to have the protein of interest expressed **concomitantly** with its fusion derivative so that the latter would protect it against proteolysis. Thus, document (46) dealt with a completely different problem (protein stabilisation) from that dealt with in the patent in suit. It could only be with hindsight that its teachings would be combined with those of document (7). The subject-matter of claim 13 was inventive.

Consent was not given to discussing inventive step or insufficiency in relation to claim 1.

XI. The Appellants requested that the decision under appeal be set aside and as main request that the European patent No. 0 564 531 be revoked, or as first auxiliary request that the case be remitted to the first instance for further examination or as second auxiliary request that the following question submitted at the oral proceedings on 5 February 2004 be referred to the Enlarged Board of Appeal:

"The Enlarged Board established in G 10/91 that only those grounds for opposition already cited at the opposition stage could be considered on appeal. New ones could be introduced only with the consent of the patentee, whose power of veto applied regardless of their relevance. Does this apply even where the patentee, in his defence to one ground of opposition, raises an issue which has an adverse implication for the validity of the patent under a ground which has not been pleaded ?"

The Respondents requested that the appeal be dismissed.

Reasons for the decision

Admissibility of 15 new documents in the proceedings

1. On 29 January 2004, ie seven days before the oral proceedings, the Respondents filed seven new documents. The time limit of one month before the oral proceedings set up by the Board for the filing of new submissions was not observed. These documents are considered to be late filed and, thus, are not admitted in the proceedings.

2. On 5 January 2004, ie within the time limit set up by the Board, the Appellants filed five new documents and three declarations.
3. One of these declarations is an expert's opinion on the inherent content of the passage on page 48, lines 37 to 48 of document (1). It does not bring any useful information in addition to that already on file. The other two declarations include new experimental data which in accordance with the case law (cf, for example, T 397/02 of 10 October 2003, see in particular point 2 of the reasons), should not be admitted at this late stage. For these reasons, the Board decides not to admit any of them in the proceedings.
4. Four of the documents are post-published. They are meant to throw light on the inherent content of the above mentioned passage which is argued to destroy the novelty of the method of claim 1 under Article 54(3)(4) EPC when this inherent content is taken into account.
5. In accordance with Article 54 EPC, the only kind of documents which may be taken into consideration when assessing novelty are those belonging to the state of the art at the date of filing and those European patent applications which were filed before that date and published thereafter. If it is necessary to refer to the above mentioned four documents, this could only be because they add information not present in document (1). If it is not necessary to refer to them, it would be unsafe to do so and merely confuse the issue as they are post-published documents which cannot themselves be

used in assessing novelty. Consequently, the four post-published documents are not admitted in the proceedings.

6. The Appellants' argument that proving the inherency of a given feature in a method disclosed under Article 54(3)(4) EPC necessarily required the use of post-published documents is not convincing. According to the consistent view in the case law on novelty, when considering how far the teaching in a written description of an allegedly novelty-destroying document also makes available certain features which are not explicitly stated, ie implicit or intrinsic features, all that matters is the **whole contents** of the said document alone as **read and interpreted** by the skilled person on the background of common general knowledge, ie the knowledge generally available at the relevant filing date, **not** later. This excludes the consideration of post-published documents even for assessing background common general knowledge at the priority date. This principle must also apply to situations where novelty under Article 54(3)(4) EPC has to be assessed. In this context, it is noticed that bacteriophage display was a technique already known in the art at the priority date (patent in suit, passage bridging pages 2 and 3).

7. Document (46) belongs to the prior art, it was submitted in the context of assessing inventive step because it disclosed an expression plasmid vector, ie pEH-90-10am (column 20, line 5 onwards), which comprises a first and second genes separated from each other by a suppressible terminator codon. In view of the similarity between the structure of this plasmid and that of the phagemid DNA in claim 13, it was

decided to accept the document in the proceedings so that its relevance could be assessed in more detail.

Article 54(3)(4) EPC; novelty

Claim 1

8. Document (1) was argued to be novelty destroying for the subject-matter of claim 1 under Article 54(3)(4) EPC. The teachings of said document which may be taken into account are those also contained in its third priority document: GB 9024503.6 with a filing date of 12 November 1990 since the earliest priority date of the patent in suit is 3 December 1990.

9. Both document (1) and GB 9024503.6 relate to the production of viral particles having the ability to present antibodies or receptor molecules at their surface and to various methods of use of said particles. It is thus disclosed that:

(a) "*...., a cDNA library could be constructed and inserted into the bacteriophage and this library be screened for the ability to bind a ligand.*" (GB third priority document: page 8, lines 8 to 12, corresponding passage in document (1): page 11, lines 45 to 49).

(b) "*... the present invention also provides novel screening systems and assay formats. In these systems and formats, the gene sequence encoding the binding molecule (eg the antibody) of desired specificity could be separated from the general population having a range of specificities by the fact of its binding to a specific target (eg antigen or*

epitope)" (GB third priority document: page 11, lines 31 to 37; corresponding passage in document (1): page 21, lines 45 to 51).

(c) *"A useful and novel set of applications makes use of the binding protein in the phage to target the phage genome to a particular cell or group of cells"*. (GB third priority document: page 8, lines 21 to 25; document (1): page 12, lines 23 to 25).

(d) *"... a specific receptor could be expressed on the surface of the phage so that it could bind its ligand. The receptor could then be modified by, for example, in vitro mutagenesis and variants having higher binding affinity for the ligand selected."*

(GB third priority document: page 7, lines 14 to 17; corresponding passage in document (1): page 10, lines 23 to 25). The same approach is also disclosed in relation to antibody display (GB third priority document: passage bridging pages 6 and 7, corresponding passage in document (1): page 7, lines 15 to 18).

10. Examples common to both document (1) and the third priority document comprise:

(a) the construction of vectors facilitating the cloning of various foreign DNA sequences (Examples 1 and 5 in both documents).

(b) the insertion of foreign DNA sequences in the bacteriophage vector (Examples 2, 3, 9, 11, 13 and 15 in document (1) corresponding to Examples 2, 3, 9, 13, 15 and 11 in the GB priority document).

(c) experiments for testing the properties of the foreign protein once expressed at the bacteriophage surface (Examples 4, 6, 7 and 12 in document (1) corresponding to Examples 4, 6, 7 and 14 in the GB priority document).

(d) the isolation of a preferred recombinant bacteriophage from a mixture (Examples 8 and 10 in both documents).

11. A passage referring to phagemids is found in Example 1 (GB third priority document: page 25, lines 4 to 14; document (1)): page 48, lines 37 to 48) which reads as follows:

"Clearly alternative constructions will be apparent to those skilled in the art. For example, M13 and/or its host bacteria could be modified such that its gene III could be disrupted without the onset of excessive cell death; the modified fd gene III, or other modified protein, could be incorporated into a plasmid containing a single stranded phage replication origin, such as pUC119, superinfection with modified phage such as K07 would then result in the encapsulation of the phage antibody genome in a coat partially derived from the helper phage and partly from the phage antibody gene III construct."

12. It is on the basis of this sole passage in document (1) that the method of claim 1 was argued by the Appellants not to be novel. It is immediately apparent that no explicit disclosure is provided of a method step corresponding to step (b) of the method in claim 1: *"mutating the vector at one or more selected positions*

within the first gene thereby forming a family of related plasmids.". This fact is not contested by the Appellants who argue that when reading the description as a whole, the skilled person would necessarily understand this step to be included in the method described on page 48 since it was described on pages 7 and 10 in relation to using bacteriophages.

13. This argument is not found convincing. As mentioned in point 9 supra, document (1) as a whole describes at least four methods making use of bacteriophage display. Only one of them (method (d); point 9 supra) requires that the foreign DNA (encoding a receptor or an antibody) be mutated once present in the bacteriophage DNA; the three other methods (methods (a) to (c) supra) do not necessitate such a step. Furthermore, Example 1 which the passage on page 48 belongs to, only mentions mutagenesis in the context of constructing new appropriate vectors. As for the other examples, none of them are concerned with the mutagenesis of the DNA encoding the fusion protein (point 10, supra).

14. For these reasons, the skilled person would not directly and unequivocally derive from reading document (1) as a whole that a step of mutagenesis necessarily is present when constructing either bacteriophages or phagemids for the purpose of protein display. These findings are sufficient to conclude that document (1) does not clearly and unambiguously disclose a method as claimed in claim 1 comprising step (b) and that therefore, it cannot destroy the novelty of the subject-matter of said claim.

15. Having reached this conclusion on the basis of step (b), there is no need for the Board to investigate whether or not the other steps of the claimed method are disclosed in the passage on page 48, lines 37 to 48 of document (1).

Claims 22 and 26

16. These claims relate to methods which comprise a mutagenesis step corresponding to step (b) of the method of claim 1. If only for this reason their subject-matter is novel.
17. The subject-matter of the granted claims fulfils the requirements of Article 54 EPC.

Article 56 EPC; inventive step

Claim 13

18. The closest prior art is document (7) which describes an enrichment method for variant proteins with altered binding properties. The gene encoding human growth hormone is fused to the 3' end of the gene III encoding a minor coat protein of bacteriophage M13. The hybrid construct is cloned into a plasmid containing origins of replication for E.coli and for filamentous phage. Upon superinfection of the bacterial host carrying the recombinant plasmid with bacteriophage M13 K07, phagemid particles are produced which usually carry no more than one copy of the fusion protein along with four copies of wild-type gene III on their surface.

19. Starting from the closest prior art, the problem to be solved is defined as producing alternative phagemids for protein display. The need for different phagemids is not suggested in document (7). Yet, the Board derives from reading the background art as summarized in the patent in suit that at the priority date, it was of great concern to the scientific community to develop several efficient screening systems for binding molecules. Thus, it is accepted that the formulation of this problem would have been obvious to the person skilled in the art.

20. The solution given in claim 13 consists in phagemids the DNA of which includes the gene of interest fused to the gene encoding at least part of a coat protein **with a suppressible codon being inserted at the junction in the gene fusion**. A suppressor⁻ host containing the phagemid DNA expresses the protein of interest in unfused form. When superinfected with a filamentous phage, a suppressor⁺ host containing the phagemid DNA produces phagemid particles which carry the protein of interest on its surface because said protein is expressed as part of the coat protein. Thus, by using one phagemid expression vector, one is able to produce the protein of interest as well as to test its binding properties. The claimed phagemids are, thus, distinctly advantageous over those disclosed in document (7).

21. The Appellants argued that this improvement would have readily come to the skilled person's mind taking into account the teachings of document (46). As already mentioned in point 7 above, this document was accepted into the proceedings as prima facie possibly relevant because it disclosed a plasmid which carried a DNA

fragment with the same structure as that present in the phagemid particles of claim 13, ie wherein a gene of interest is fused to a "carrier" gene, a suppressible codon being inserted at the junction in the fusion (pEH-90-10am, column 20). An in-depth reading of the document shows that this construct is expressed in a suppressor⁺ host in order to produce the protein of interest, simultaneously in fused and unfused forms. In fact, as the purpose of the experiment is **to stabilize** the unfused form by co-aggregation with the fused form, an essential part of the concept underlying the experiment is that the two forms must be expressed in the same host.

22. Document (46) does not relate to the field of phagemid display nor to the field of gene expression per se: it is rather concerned with protein stabilisation once the protein has been expressed. The above mentioned concept is not relevant to the invention as claimed in claim 13. Indeed, the fact that when the phagemid DNA is present in a suppressor⁺ host, fused and unfused proteins are most probably concomitantly produced was never argued to have a bearing on the display on the phage surface.
23. For these reasons, the Board concludes that, even if the skilled person had come across document (46) while working in the field of phage display (which is not entirely certain), he/she would have had no incentive to combine its teachings with those of document (7) in order to isolate alternative phagemids to those described in this last document.
24. There is no other documents on file the teachings of which could be combined with those of document (7) to

make obvious the subject-matter of claim 13. Inventive step is, thus, acknowledged.

Issues raised for the first time on appeal

Inventive step of claim 1

25. In the opposition proceedings, the only ground under which the validity of claim 1 had been challenged was lack of novelty over document (1), which was part of the state of the art only under Article 54(3) EPC. Pursuant to Article 56 EPC, document (1) is not to be considered in deciding whether there has been an inventive step so there can be no basis for alleging that an attack in the opposition proceedings based on lack of novelty over document (1) was also implicitly an attack on the ground of inventive step.
26. As made clear in decisions G 1/95 and G 7/95 of the Enlarged Board of Appeal (OJ EPO 1996, 615 and 626 respectively) when expanding on what had already been said in opinion G 10/91 (OJ EPO 1993, 420), the totality of Articles (namely Articles 52 to 57 EPC) within the meaning of Article 100(a) EPC do not constitute a single objection to the maintenance of the patent, but a collection of different objections. Further a fresh ground for opposition is to be interpreted as referring to a new legal basis for objecting to the maintenance of the patent, which was not both raised and substantiated in the notice of opposition and which was not introduced into the proceedings by the opposition division.

The attack of lack of novelty does not have the same legal basis as the attack of lack of inventive step, though, as stated in decision G 7/95, lack of novelty in relation to documents which are prior art pursuant to Article 54(2) EPC is also relevant when assessing the legal ground of lack of inventive step.

27. The Board concludes that in this case attempting to argue for lack of inventive step of claim 1 on appeal amounts to raising a fresh ground of opposition. The situation is not analogous to one in which the ground of inventive step had been originally alleged and substantiated, and the appellant merely seeks to rely on other or additional documents. Nor does the fact that in the opposition proceedings lack of inventive step was argued against independent claim 13 assist the Appellants, since it remains the fact that no attack of lack of inventive step against the claim now under consideration, claim 1, had been raised, let alone substantiated, in the opposition proceedings.

28. Since the Respondents have not given consent to consideration of the issue of lack of inventive step of claim 1, it cannot be considered in the appeal proceedings. The Board would in any case have been reluctant to consider an issue which does not appear to have been properly substantiated even in the appeal proceedings.

Insufficiency in relation to claim 1

29. Insufficiency in relation to claim 1 was not raised, let alone substantiated, during the opposition proceedings. Since the Respondents have not given

consent to consideration of this issue, it cannot be considered in the appeal proceedings.

30. The case put forward would in any case not appear to be one that the subject matter of claim 1 cannot be carried out. Not even the Appellants have seriously argued this. Rather the Appellants used it in the form of a squeeze argument when arguing lack of novelty: either claim 1 and document (1) both disclosed the same process, in particular feature (e) and thus, document (1) was detrimental to the novelty of claim 1, alternatively, if document (1) did not disclose feature (e), then in the same manner, the patent in suit did not provide an enabling disclosure of said feature. However the Board's finding of novelty is based on feature (b) of claim 1 not being found in document (1), so this squeeze argument is not enough to establish lack of sufficient disclosure.

Reference of a question to the Enlarged Board of Appeal

31. What can or cannot be considered on appeal has already been made clear in Enlarged Board opinion G 10/91 and decisions G 1/95 and G 7/95, above referred to, and following the reasoning of these decisions it is clear that attacks of lack of inventive step and insufficiency against claim 1 cannot be considered in this appeal. Since the law is clear the Board sees no occasion for the referral of any question to the Enlarged Board of Appeal.
32. Regarding the specific question suggested by the Appellants, the Board does not accept that the patentee-respondent here has raised in its defence to

one ground of opposition an issue which has an adverse implication for the validity of the patent under a ground which has not been pleaded.

Remittal to the first instance

33. The Board sees no issue here that requires remittal to the first instance for further prosecution, nor any reason for setting aside the decision under appeal.

34. The Appellants refer to decision T 1066/92 of 5 July 1995. Only the legal context of that decision is of relevance, not the technical details involved. The opposition there was directed only to granted claims 3 to 5. The opposition division maintained the patent only on the basis of granted claims 1 and 2, while refusing granted claims 3 to 5 for lack of novelty, and claims 6 to 10 for lack of inventive step. On appeal the patentee-appellant argued for the allowability of a claim combining the features of granted claims 3 and 5 on the basis of new evidence relating to the special meaning that a person skilled in the art would attribute to a test in such claim, and for the allowability of claims 6 to 10 as not being subject of the opposition. The respondent sought to introduce as a new issue the ground of insufficiency against the claim combining claims 3 and 5 as granted, justifying the lateness of this argument because the objection only became apparent as a result of the new evidence on the meaning of the test, first put forward by the patentee on appeal.

35. The competent board in case T 1066/92 held, following G 9/91 (OJ EPO 1993, 408 having the same text as, but a

different order than, G 10/91 referred to above) that the revocation of claims 6 to 10 was ultra vires the powers of the opposition division, and that the board could not itself consider the new ground of insufficiency without the consent of the appellant. However it exercised its discretion under Article 111(1) EPC to remit the case to the opposition division for further prosecution, pointing out that before novelty and inventive step were considered, the objection of insufficiency under Article 100(b) EPC which appeared prima facie highly relevant should be decided, and that under the principles laid down in G 9/91 the opposition division did have the power to raise on its own motion a ground for opposition not covered by the statement pursuant to Rule 55(c) EPC.

36. The board thus had reasons for setting aside the decision under appeal, and it also exercised its discretion under Article 111(1) EPC to remit a claim for further prosecution that had in effect been revoked for lack of novelty by the opposition division, but which on the basis of new evidence filed on appeal might be found allowable subject to consideration of insufficiency, novelty and inventive step.

37. Decision T 1066/92 certainly cannot be taken as establishing or even advocating any principle that a newly raised ground which a board of appeal cannot itself consider should be remitted to the opposition division for consideration. Such remittal must remain a matter for the discretion of the board considering each individual case. In the present case the Board sees no reasons for setting aside the decision under appeal,

and no case which requires remittal to the first instance.

Order

For these reasons, it is decided that:

1. The request for referral of a question to the Enlarged Board of Appeal is refused.
2. The appeal is dismissed.

The Registrar

The Chairman

A. Wolinski

L. Galligani