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Bezeichnung der Erfindung: Method of making a selected protein
Title of invention:
Titre de l'invention :

Klassifikation / Classification / Classement : C12P 21/02

ENTSCHEIDUNG / DECISION

vom / of / du 31 August 1990

Anmelder / Applicant / Demandeur :

Patentinhaber / Proprietor of the patent /
Titulaire du brevet : President and Fellows of Harvard College

Einsprechender / Opponent / Opposant : 01) Hoechst AG
02) Unilever N.V.
03) Gist-Brocades N.V.

Stichwort / Headword / Référence : Fusion proteins/HARVARD

EPÜ / EPC / CBE Articles 54, 56 and 83

Schlagwort / Keyword / Mot clé : "Sufficient disclosure of an example - common general knowledge"
"Novelty destroying lectures - ex officio obligation of the Board"
"Inventive step (yes)"

Leitsatz / Headnote / Sommaire

Headnote follows

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Case Number : T 60/89 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 31 August 1990

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Decision under appeal : Decision of the Opposition Division of the European Patent Office dated 6 December 1988 revoking European patent No. 0 006 694 pursuant to Article 102(1) EPC.

Composition of the Board :

Chairman : P.A.M. Lançon
Members : U.M. Kinkeldey
C. Holtz

Summary of Facts and Submissions

I. The Appellants are the proprietors of European patent 6 694 (European patent application 79 301 054.7). Claims 1 and 6 as granted read as follows:

"1. A method of making a selected protein or portion thereof by inserting DNA representing the selected protein or portion thereof into a bacterial gene, characterized by cleaving the bacterial gene for an extracellular or periplasmic carrier protein, inserting into the cleavage site by a recombinant step a non-bacterial DNA fragment which codes for the selected protein or portion thereof, transforming a bacterial host with the recombined gene, and culturing the transformed bacteria to excrete the selected protein or portion thereof.

6. A recombinant DNA molecule comprising a bacterial gene for an extracellular or periplasmic carrier protein and a non-bacterial gene which codes for a selected protein or polypeptide, said non-bacterial gene having been inserted into said bacterial gene and joined end to end with a portion thereof."

II. Notices of opposition were filed against the European patent by three parties. Revocation of the patent was requested on the grounds of Article 100(a) and (b) EPC. During the procedure before the Opposition Division altogether more than fifty documents were filed by the parties, out of which the following remained relevant in the appeal proceedings:

(Doc. A): Proceedings of the 43rd Cold Spring Harbor Symposium on Quantitative Biology, DNA: Replication and Recombination, 77-90 (Sutcliffe)

(Doc. B): Inouye and Beckwith, PNAS 74 (1977), 1440-1444

(Doc. C): Silhavy et al., PNAS 73 (1976), 3423-3427

(Doc. D): Silhavy et al., PNAS 74(1977), 5411-5415

(Doc. E): Blobel and Dobberstein, J. Cell. Biol. 67 (1975), 835-851

(Doc. F): Chang et al., PNAS 75 (1978), 361-365

(Doc. G): Bolivar et al., Gene 2 (1977), 95-113

(Doc. H): Itakura et al., Science 198 (1977), 1056-1063.

The Appellants submitted during oral proceedings before the Opposition Division a set of new claims containing two new Claims 2 and 7; said claims reading as follows:

"2. A method of making a selected non-bacterial protein or polypeptide, which protein or polypeptide is normally excreted through a membrane of the cell within which it is made in nature, by inserting DNA representing the selected protein or polypeptide into a bacterial gene, characterized by cleaving the bacterial gene for an extracellular or periplasmic carrier protein within the portion of the bacterial gene encoding the hydrophobic leader sequence of the bacterial protein such that the selected protein or polypeptide will be excreted across a bacterial cell membrane, inserting into the cleavage site by a recombinant step a non-bacterial DNA fragment which codes for the selected protein or polypeptide, transforming a bacterial host with the recombined gene, and culturing the transformed bacteria to excrete the selected protein or polypeptide through a membrane of the transformed bacteria.

7. A recombinant DNA molecule comprising a bacterial gene for an extracellular or periplasmic carrier protein and a non-bacterial gene which codes for a selected protein or polypeptide, which protein or polypeptide is normally excreted through the membrane of the cell within which it is made in nature, said non-bacterial gene having been inserted into said bacterial gene within the portion of the bacterial gene encoding the hydrophobic leader sequence of the bacterial protein and joined end to end with a portion thereof."

III. The Opposition Division revoked the patent on the ground of insufficiency under Article 83 EPC of the subject-matter of Claims 2 and 7.

According to the Opposition Division's opinion the description in column 8, lines 3 to 43, represented a working example and had to lead to success when repeated by a skilled person. According to all facts and submissions on file during the opposition procedure it was, however, not plausible that the process of Claim 2 as further described in said column 8 could easily be accomplished. Therefore, the description was insufficient.

The recombinant DNA, as claimed in Claim 7, being an essential step in the process of Claim 2, was likewise not sufficiently described.

Novelty and inventive step were acknowledged.

IV. The Appellants lodged an appeal against the decision and submitted a statement of grounds.

During the appeal proceedings they filed two new sets of claims, of which the main set corresponds in substance to the one considered by the Opposition Division, while in the subsidiary request Claims 2 and 7 are omitted.

With supplemental statements in support of appeal, the Appellants submitted experimental data in support of their argument that a skilled person could carry out the invention as claimed in rejected Claims 2 and 7 on the basis of the disclosure in the patent in suit in column 8.

The Respondents filed various observations in response to the statement of grounds and in particular objected to the submission of experimental data by the Appellants, as being too late and impossible to be reproduced with means only available in 1978, the time of the priority date of the patent in suit.

In addition to an earlier raised novelty objection with regard to a symposium held in May/June 1978 at Cold Spring Harbor, one Respondent submitted further information about a lecture held at the University of Chicago by one of the inventors of the patent in suit, professor Walter Gilbert of Harvard University, reporting the construction of a bacteria producing small quantities of rat proinsulin in his laboratory. Evidence was provided that this work was made public in the week of 4-10 June 1978.

V. During oral proceedings on 31 August 1990 the Appellants argued essentially as follows:

(a) The experiment submitted with the supplemental statement was carried out using common general knowledge in 1978, even if restriction enzymes and/or exonucleases being different from those described in column 8 were used. It showed that according to this basic information given in column 8 of the description of the patent in suit, the detailed necessary steps, provided by common general knowledge can be taken to successfully carry out the method according to Claim 2.

(b) As to the objections raised with regard to novelty according to Article 54 EPC, Professor Gilbert repeated the content of a declaration filed during opposition proceedings, according to which it was extremely unlikely that during the mentioned Cold Spring Harbor Symposium the content of the patent in suit was presented. The argument was strengthened that there was no novelty destroying disclosure in this respect. With respect to the newly submitted objection by the Respondents (3), Professor Gilbert could not say with absolute certainty that the lecture he held at the University of Chicago was prior to the filing date of the priority document in the United States but again felt it to be extremely unlikely that this lecture was held before this filing date because he was aware of the importance to keep the invention secret before the first filing of an application in the United States. In connection with these statements attention was drawn to copies of several newspaper reports about this work.

(c) As to the inventive step required by Article 56 EPC it was argued that according to document (H), scientists succeeded in expressing a heterologous protein within a bacterial cell by fusing it to a bacterial protein. The purpose of doing so was to protect the heterologous protein from degradation within the bacterial cell by protein-degrading enzymes. There was no hint whatsoever in this document to fuse DNA coding for a heterologous protein to bacterial DNA coding for the leader sequence of a bacterial protein which was to be transported through the cell membrane into either the periplasmatic space or the extracellular medium.

The disclosure provided by documents (C) or (D) described experiments showing that bacterial proteins in the same way as eukaryotic proteins can be transported at least to the outer surface of a bacterial membrane wherein they could be located. According to the invention, contrary to the disclosure of documents (C) or (D), the heterologous gene is fused in a way described in document (H) to the leader sequence of a bacterial protein which was secreted through the membrane rather than located within the membrane.

At the time of the priority date only one method to recover desired heterologous proteins, expressed by bacterial cells was available and this method was to destroy the bacterial cell by lysis or disruption. The latter method had many disadvantages.

VI. The Respondents submitted essentially the following arguments:

(a) The experiments were carried out with restriction enzymes and exonucleases not mentioned in said column 8 and the replacement by other enzymes was either not within the skill of the persons working in the field of genetic engineering at that time, or not available at all. In this context in particular, Respondents (1) pointed out that the level of common general knowledge has to be the same when considering the requirements of Article 83 and those of Article 56, i.e. inventive step.

It was of particular importance that instead of the restriction enzyme Taq, mentioned in column 8, the restriction enzyme PvuI was used. Although this

restriction enzyme was actually available in 1978, its respective restriction site was not known in 1978 and further, nowhere on the restriction map of the plasmid pBR322, which contained the gene to be cleaved by the mentioned restriction enzyme, a restriction site for the restriction enzyme PvuI was shown. Since the amount of trial and error to carry out the method of Claim 2 anyhow was high it would not have been within common general knowledge to use a restriction enzyme whose cleaving site was not known and not mapped on the plasmid used in the description of the patent in suit. As it was, however, quite clear from the experiment submitted with the second supplemental statement that it was very important to use a restriction enzyme which cleaves the plasmid pBR322 only once. In addition, this single cleavage site has to be located in a position in relation to the bacterial leader sequence and the heterologous gene which provides a reasonable starting point for the next procedural steps as the nibbling back of a specific amount of base pairs to provide the proper sequences for the so-called perfect fusion. Furthermore, the method of "nibbling back" an exact number of base pairs was not controllable without undue burden in 1978. Professor Gilbert, one of the inventors who later was awarded the Nobel Prize, certainly could not be deemed representative of the average person skilled in the art.

Moreover, the starting plasmids mentioned in column 8 to carry out the method claimed in Claim 2 or to produce the plasmid as claimed in Claim 7, were different from that used in the experiment.

(b) The Respondents maintained the argument that the content of document (A) was a true repetition of the

symposium in Cold Spring Harbor. In particular Respondents (3) argued that document (A) was reviewed inter alia by Professor Gilbert so that it is likely that he agreed to the content of document (A) in such a way that this content was already presented at the mentioned symposium which took place before the priority date of the patent in suit.

(c) All Respondents contested an inventive step of the method of Claim 1.

VII. The Appellants request that the decision be set aside and the patent be maintained on the basis of Claims 1 to 10, (main request) or of Claims 1 to 8 (auxiliary request) and the respective sets of claims for the Contracting State Austria, both requests submitted on 18 June 1990.

The Respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. Main Request

2.1 Amendments (Article 123(2) and (3) EPC)

Claims 2 and 7 of the main request are differently worded from Claims 2 and 7 as rejected by the Opposition Division in as much as it is made clearer that the non-bacterial DNA fragment has been fused end to end to the bacterial gene within the portion of the bacterial gene encoding the hydrophobic leader sequence of the bacterial protein or a portion thereof, such that the selected protein or polypeptide will be excreted across a bacterial cell

membrane. The meaning of "a" membrane is supported by the whole content of the patent specification which does not refer solely to a certain inner membrane or outer membrane of a certain bacteria but rather to both kinds of membranes, i.e. excretion into the periplasmatic space and the extracellular medium is described; further, not only a particular bacterial strain can be used according to the description but rather strains which are likewise suitable. On the basis of the original disclosure and the claims as granted, which are also worded such that it can be understood that the proteins are excreted through "a" membrane, for example by the wording that "a" bacterial host is transformed with the recombined gene, the amended wording of Claims 2 and 7 of the main request is allowable with regard to the requirements of Article 123(2) and (3) EPC.

2.2 **Sufficiency of disclosure of Claims 2 and 7 (Article 83 EPC)**

2.2.1 The method as claimed in Claim 2 describes a "perfect fusion" between the portion of a bacterial gene encoding the hydrophobic leader sequence of an extracellular or periplasmatic carrier protein or a portion thereof to a non-bacterial DNA fragment which codes for the selected protein or polypeptide. This general approach is described in more detail in said column 8 such that, for example, "the segment of the penicillinase gene DNA between the code for amino acid 23 at the end of the hydrophobic leader and the code for amino acid 45 at the Taq cut can be removed by nibbling back the DNA by a mixture of appropriate enzymes. One such mixture is the lambda exonuclease which will chew back the DNA strand from the 5' end, together with the enzyme S1, which will remove the single stranded overhang. Another such mixture is proposed which is T_4 DNA polymerase which will chew back the 3' end of one DNA strand together

with S1, which again will remove the single stranded overhang. By controlled digestion the plasmid's DNA molecule can be appropriately shortened to the fragment extending from the R1 cut to the point coding for amino acid 23 or to other points on the hydrophobic leader sequence, and such a fragment can be fused to a similarly generated fragment containing the insulin sequence, chewed back enzymetically to a convenient initial point, presumably again, the point where the mature insulin molecule begins. These two fragments can be fused together, for example, by butt end ligation by the T_4 DNA ligase and that fusion inserted into the plasmid". In column 8 it is further stated that, "although such construction can in principle be done exactly, in practice they will probably be done on a random basis, involving the splicing of a variety of gene fragments whose end points are in interesting regions".

2.2.2 When considering whether or not the average skilled person at the time of the priority date of the patent in suit would have been able to carry out the process of Claim 2 according to the description of column 8, it seems to be necessary to define the skilled person and common general knowledge in the field of genetic engineering in 1978. One has to examine whether the information given in column 8 can be understood as a working example. Further, one has to clarify whether there may have been variants of all specific means as described in column 8 available within common general knowledge and would thus have enabled a skilled person to reproduce the process of Claim 2, according to the general teaching of column 8.

2.2.3 As to the question of "working example", raised above, the wording of the description in column 8 using words such as "presumably", "probably", "will be" and "in principle" indicates that the work described has not yet been done.

One can, therefore, hardly interpret the information in column 8 as a working example. According to the Board's opinion the arguments put forward by the Respondents that, if the skilled persons had worked exactly according to the rather vague information provided in column 8 in the sense of a working example, within a reasonable amount of time and investigation, they would have failed, are convincing. In particular in 1978, as emphasised by the Respondents, cleaving the penicillinase gene with the Taq restriction enzyme would have produced seven fragments and at that time it would have been extremely difficult to handle this problem. Further, the control over the enzymes nibbling back the DNA was not yet well developed so that it would have been very cumbersome to stop the reaction mixture exactly at that point where it was necessary to form a perfect fusion. Thus, the proposal given in column 8 would not have enabled a skilled person to carry out the process of Claim 2 when working exactly along the wording of this part of the description, without undue burden, if at all.

2.2.4 To answer the question whether or not there had been variants of the means and process steps mentioned in column 8 known to the skilled person which then would have enabled him to carry out the invention according to Claim 2, one has to find out what was within common general knowledge at that time which was available to a skilled person. Apparently the penicillinase gene in the plasmid pBR322 was known and restriction enzymes had been on the market. Further, exonucleases were known which nibble back the DNA once cut with a restriction enzyme. The Board, however, agrees with the arguments of the Respondents that, for example, replacing the restriction enzyme Taq, which apparently is unsuitable for carrying out the invention, by a more suitable restriction enzyme, namely PvuI, as used by the Appellants in their experiment in their supplemental statement, was not a variant available for the skilled

person within common general knowledge. It was made clear by the Respondents during the oral proceedings that, although the restriction enzyme PvuI was available as such, the skilled person would not have used it because the known and published restriction map of the plasmid pBR322 did not show the site for this restriction enzyme. One cannot, therefore, reasonably assume that the skilled person would have used this mentioned restriction enzyme even if one agrees with the Appellants' opinion that in any kind of these experiments scientists use a battery of restriction enzymes to evaluate the most suitable ones. Precisely in this situation it seems that it would have been unlikely to select a restriction enzyme whose cleavage characteristics were not known, be it the number or the location of the sites. In choosing the suitable restriction enzyme in each case there lies apparently a considerable amount of skill and trial and error. It is the opinion of the Board that the skilled person in the field of genetic engineering in 1978 is not to be defined as a Nobel Prize laureate, even if a number of scientists working in this field at that time were actually awarded the Nobel Prize. Rather, it is understood that the skilled person was to be seen as a graduate scientist or a team of scientists of that skill, working in laboratories which developed from molecular genetics to genetic engineering techniques, at that time.

2.2.5 The experiment submitted by the Appellants furthermore shows that the method of chewing back the respective DNA fragments for a precisely defined amount of base pairs again was carried out with exonucleases being different from those mentioned in column 8. This again indicates that an amount of skill being beyond that of the average graduate scientist is necessary to choose a mixture of exonucleases which reduces the amount of random experiments for producing exactly the desired DNA fragments to a reasonable level which can be estimated as routine experiments in this field at that time.

2.2.6 A further step, necessary for the production of a "perfect fusion", is described in the experiment. This is the preparation of two different fragments of the plasmid, the one containing the bacterial hydrophobic leader sequence which has to be nibbled back to remove exactly 348 base pairs and a second fragment comprising the proinsulin leader sequence which has to be nibbled back to remove exactly 209 base pairs. These fragments then have to be religated with the remaining part of the plasmid to perform the "perfect fusion" plasmid. This is necessary because the distance to be nibbled back from the initial point of the PvuI cleavage site is different in both directions and therefore cannot be done in one single assay. As to this step there is apparently a gap in the description of column 8 and it is the Board's opinion that it was not within common general knowledge to fill in this gap at the time of the priority date in 1978.

2.2.7 In the decision T 292/85 (OJ EPO 1989, 275) the Board had concluded that it is not necessary for a sufficient disclosure of a claimed process that each and every variant can be carried out as long as there are variants available within common general knowledge. In the present case neither was it within common general knowledge to find variants suitable to carry out the method proposed in column 8 nor was it likely that a skilled person would have been successful in reproducing the method of Claim 2 when working exactly according to the wording of column 8. Claim 2 is, therefore, not allowable according to Article 83 EPC.

The product claimed in Claim 7 corresponds to the process of Claim 2 in as much as it represents a step in the process of Claim 2. The reasoning for non-allowability of Claim 2 with regard to Article 83 EPC also applies to Claim 7.

The main request, containing non-allowable Claims 2 and 7, therefore has to be rejected.

3. Auxiliary Request

3.1 Novelty (Article 54 EPC)

3.1.1 With regard to the June 1978 lecture held by Professor Gilbert at the University of Chicago the Respondents have declared, after having taken into account the submissions presented by the Appellants during the oral proceedings, that they do not doubt this information. However, in the Board's view the newspaper failed to clarify definitely the date. In the Board's opinion, in a situation like the present one, where the disputed facts had occurred twelve years ago and the opposition proceedings already started six years ago, and furthermore where the question is not pursued by the parties, the Board no longer has the obligation to investigate this situation ex officio with regard to Article 114(1) EPC. Therefore the Board accepts that said lecture before the University of Chicago does not destroy novelty of the patent in suit.

3.1.2 The same conclusion holds true for the lecture held by Mr Sutcliffe at the Cold Spring Harbor symposium before the priority date of the patent in suit. During oral proceedings before the Opposition Division, the patentee filed a declaration of one of the inventors, Professor Gilbert stating that it was not likely that the subject-matter of a lecture held by a member of his laboratory at Harvard University, Mr Sutcliffe, described the work of Professor Gilbert's group on the expression and secretion of rat proinsulin. Rather, the topic of Mr Sutcliffe's lecture was the complete nucleotide sequencing of the plasmid pBR322. A further strong indication that Mr Sutcliffe did not speak about the subject-matter of the

patent in suit was that Mr Sutcliffe, knowing that Professor Gilbert was preparing to announce his work on rat proinsulin himself in Chicago in early June, would not have announced this work first. During the oral proceedings, these statements were reiterated with the addition that Mr Sutcliffe did not work on rat proinsulin.

Although document (A) seen separately would have been an indication of what was the topic at the Cold Spring Harbor symposium, on balance, and in the absence of any further evidence, the Board finds this symposium not novelty destroying.

Thus, Claim 1 of the auxiliary request is novel.

3.2 **Inventive Step (Article 56 EPC)**

3.2.1 To investigate the problem underlying the patent in suit the Board considers document (H) to be the closest prior art. This document describes research work in the same field of technique to which the patent in suit relates. In the case of document (H) a gene for somatostatin, a mammalian peptide with 14 amino acid residues was synthesised in total by chemical methods. This gene was then fused to the ß-galactosidase gene of a bacterium, Escherichia coli on the plasmid pBR322. Expression within a bacterial cell of this fused gene led to the synthesis of a polypeptide including the sequence of amino acids corresponding to somatostatin. Having been recovered from the bacterial cell, the large chimeric protein was cleaved to produce active somatostatin. These results represented the first success in achieving expression (that is, transcription into RNA and translation of that RNA into a protein of a desired amino acid sequence) of a gene of chemically synthesised origin. The molecule prepared appears to be relatively resistant to endogenous

proteolytic activity. This method apparently protects many proteins in E.coli, whether large enzymes or smaller polypeptides, from degradation which otherwise would be undetectable for this reason. The heterologous protein, expressed and produced as a fusion protein has to be recovered from the bacterial cells. This is done in document (H) by destroying the bacterial cells and isolating the desired protein from the cellular debris.

3.2.2 During the proceedings the Appellants emphasised the drawbacks of the known process to isolate heterologous proteins. As convincingly submitted by Professor Gilbert, after destruction of the bacterial cell the main difficulty arising with purification of the desired protein is the contamination by hundreds of other proteins contained in the bacterial cell. Starting from document (H) the problem underlying the patent in suit thus can be seen in improving the isolation of heterologous protein expressed in a host cell.

3.2.3 This problem is solved in the patent as described in Claim 1 by fusing the heterologous gene to a bacterial gene, coding for a portion of a bacterial extracellular or periplasmatic carrier protein by a recombinant step so that the fused protein is excreted through a membrane of the cell within which it is made in nature so that the excreted selected fusion protein or fusion polypeptide can be recovered from the extracellular medium. The example described in the patent in suit provides evidence that the problem was actually solved by the patentees. Sufficiency of disclosure of Claim 1 and the corresponding part in the description was in any event never contested by the Respondents.

3.2.4 The claimed method has advantages over the closest prior art method described in document (H) as it ensures stability of the desired heterologous protein within the cell likewise to the method described in document (H) and in addition transports the desired protein to the cell membrane and through the cell membrane, whereby firstly the leader sequence of the bacterial protein is cleaved already from the fused protein by bacterial enzymes located in the bacterial membranes and further recovery of the desired protein is facilitated because, compared to the totality of proteins within a bacterial cell, the number of proteins secreted into the cell surrounding medium is remarkably decreased. The method of Claim 1, thus, provides an elegant development of the method described in document (H).

3.2.5 The question is whether, starting from document (H), this method was obvious to a skilled person with regard to the knowledge disclosed by documents (C), (D) or (F). Apparently the knowledge of the mentioned documents provides a tool for the claimed method. This does not, however, in the Board's opinion, necessarily mean that using this tool in a method described elsewhere renders the whole process obvious.

The Board adopts the view that the same level of skill has to be applied when, for the same invention, the two questions of sufficient disclosure and inventive step have to be considered. As has been pointed out above under point 2.2.4, it was not the Nobel Prize laureate's level of skill which determines the person skilled in the art and hence what must be considered as falling within common general knowledge at that time. One may assume that a skilled person, as defined above (see point 2.2.4), being confronted with this problem, knew about the existence of the leader sequences in eukaryotic cell systems and the signal hypothesis in bacterial systems. They may equally

have been aware of documents (C), (D) and (F) which showed that the signal hypothesis might be true for bacterial proteins as well. It has to be mentioned here that, although the said documents describe proteins which are carried to the membrane, apparently by leader sequences, these proteins are not secreted through the membrane into the area surrounding the membrane but rather are components of the membrane itself, although localised with their functional parts at the outer surface of the membrane. The necessary steps to be taken to arrive at the method of Claim 1, based on all knowledge mentioned, were firstly to come upon the idea that the fusion of the heterologous protein to the leader sequences of a bacteria protein will have the mentioned advantages; there is no proposal whatsoever in this respect in any of the prior art documents; secondly, to choose a suitable bacterial protein having a leader sequence. The key question therefore is whether it was obvious for a skilled person to try the idea outlined above with a reasonable expectation of success.

3.2.6 As pointed out above under paragraph 2.2, in the Board's opinion it was not within common general knowledge at the time of the priority date to be aware of the necessary detailed steps and variants to carry out the process of Claim 2 according to the information given in column 8. Applying the same principle here would require skills beyond common general knowledge and the amount of trial and error which could be expected to have to be used by a skilled person at that time to combine the method described in document (H) with one of the documents describing the existence and function of bacterial leader sequences would have been excessive. To use known tools in a suitable combination to carry out a new method does not necessarily render this method obvious.

3.2.7 This opinion is supported by the fact that none of the documents of the prior art gives any advice how to isolate heterologous proteins from host cells other than by destroying the cells. As emphasised by Professor Gilbert during the oral proceedings, to date there are still only two alternatives: to disrupt or lyse the cells and recover the desired protein from the cell debris; or to fuse the heterologous protein to a bacterial leader sequence protein and actively secrete the desired protein through the membrane into the space surrounding the bacterial cell with all the advantages mentioned above.

For the reasons cited above the method of Claim 1 involves an inventive step.

Claims 2 to 8 of the auxiliary request relate to certain preferred embodiments and there are no objections to these claims.

Order

For these reasons, it is decided that:

1. The decision of the Opposition Division is set aside.

2. The patent is maintained on the basis of the auxiliary request, including a separate set of claims for Austria, submitted on 18 June 1990.

The Registrar: The Chairman:

M. Beer P. Lançon

2.11.90

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