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D E C I S I O N
of 24 May 2000

Case Number: T 0400/97 - 3.3.4

Application Number: 84301996.9

Publication Number: 0120694

IPC: C12N 15/63

Language of the proceedings: EN

Title of invention:
Processes for the production of multichain polypeptides or proteins

Patentee:
Celltech Therapeutics Limited

Opponents:
Boehringer Ingelheim GmbH
Genentech, Inc.
Eli Lilly and Company
Pharmacia & Upjohn AB
Protein Design Labs, Inc.
Roche Diagnostics GmbH

Headword:
Immunoglobulins/CELLTECH

Relevant legal provisions:
EPC Art. 83, 87, 88

Keyword:
"Oral presentation - state of the art (no)"
"Main request - sufficiency of disclosure (no)"
"First auxiliary request - sufficiency of disclosure (yes)"
"First auxiliary request - priority right (yes)"
"First auxiliary request - novelty and inventive step (yes)-not disputed"

Decisions cited:
G 0002/98, T 0081/87, T 0296/93, T 0409/91, T 0435/91, T 0890/96

Catchword:
The information content made publicly available by a lecture cannot be put beyond reasonable doubt by any evidence of the lecturer alone, as the lecturer is in a quite different position to a member of the audience (see point 3 ff).

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Case Number: T 0400/97 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 24 May 2000

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Decision under appeal: Interlocutory decision of the Opposition Division of the European Patent Office posted 14 February 1997 concerning maintenance of European patent No. 0 120 694 in amended form.

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
S. C. Perryman
L. Galligani
W. Moser

Summary of Facts and Submissions

I. European patent No. 0 120 694 with the title "Processes for the production of multichain polypeptides or proteins" was granted with 19 claims based on European patent application No. 84 301 996.9, claiming priority from GB 8308235 of 25 March 1983.

II. Seven notices of opposition were filed. By a decision within the meaning of Article 102(3) EPC dated 14 February 1997, the Opposition Division maintained the patent in amended form on the basis of the eighth auxiliary request then on file.

III. Appellants I (Patentees) and Appellants II (Opponents 02) lodged an appeal against the decision of the opposition division, paid the appeal fee and filed statements of grounds of appeal. Respondents II (Opponents 03) also lodged an appeal but later withdrew their opposition.

IV. Exchanges of submissions took place between Appellants I, Appellants II and Respondents I, III to VI (Opponents 01, 04 to 07). A communication was sent by the Board drawing attention to the fact that four of the parties involved in these proceedings were also involved in the proceedings in case T 1212/97, and suggesting that both proceedings be treated together. The parties consented to this.

V. The Board sent a communication pursuant to Article 11(2) of the Rules of Procedure of the Boards of Appeal, conveying its preliminary, non-binding opinion. Further exchanges of submissions followed.

VI. Oral proceedings in this case and in case T 1212/97 took place on 22 and 24 May 2000. On the first day, the issue of the relevance for the present case and for case T 1212/97, of the oral disclosure by Dr Shulman (document 3.4) was decided. The proceedings then continued on 24 May 2000 with all the issues to be dealt with in this case, the main claim request by Appellants I being the claims as granted. A first auxiliary claim request was also filed in the course of the oral proceedings on 24 Mai 2000.

VII. Claim 1 as granted read as follows:

"1. A process for producing a heterologous Ig molecule or an immunologically functional Ig fragment in a single host cell, which comprises transforming the host cell with separate DNA sequences respectively encoding polypeptide chains comprising at least the variable domains of the Ig heavy and light chains and expressing each of said polypeptide chains separately in said transformed single host cell."

Claims 1, 6 and 8 of the first auxiliary request read as follows:

"1. A process for producing a heterologous Ig molecule or an immunologically functional Ig fragment in a single **yeast** host cell, which comprises transforming the host cell with separate DNA sequences respectively encoding polypeptide chains comprising at least the variable domains of the Ig heavy and light chains and expressing each of said polypeptide chains separately in said transformed single **yeast** host cell."(amendments compared to claim 1 as granted emphasized by the Board).

"6. The process of anyone of claims 1 to 5, wherein the polypeptide chains are secreted by the host cells."

"8. The process of anyone of claims 1 to 6, for producing an Ig molecule or fragment having at least one constant domain, wherein the or each constant domain is derived from a source different from that from which the variable domain to which it is attached is derived."

Dependent claims 2 to 5, 7, 9 to 12 related to embodiments of the process of claim 1. Claims 13 and 14 were directed to vectors for use in said process. Claim 15 was directed to a yeast host cell transformed by the vector of claim 13 or claim 14. Claim 16 was directed to a yeast host cell transformed by two separate vectors respectively comprising a DNA sequence encoding a polypeptide comprising at least the variable domain of the Ig heavy chain and a DNA sequence encoding a polypeptide comprising at least the variable domain of the Ig light chain.

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

1.36: Hieter, P.A. et al., Cell, Vol. 22, pages 197 to 207, 1980,

1.40: Early, P. and Hood, L., in "Genetic Engineering; Principles and Methods", Setlow and Hollaender, Eds.,Plenum Press, N.Y., Vol. 3. pages 157 to 188, 1981,

1.61: Falkner, F.G. and Zachau, H.G., Nature, Vol. 298, pages 286 to 288, 15 July 1982,

1.67: EP-A-0 055 945,

1.69: Rice, D. and Baltimore, D., Proc. Natl. Acad. Sci. USA, Vol. 79, pages 7862 to 7865, December 1982,

1.76: Gunge, N., Ann. Rev. Microbiol., Vol. 37, pages 253 to 276, 1983,

1.79: Oi, V.T. et al., Proc. Natl. Acad. Sci. USA, Vol.80, pages 825 to 829, February 1983,

1.86: Ochi, A. et al., Nature, Vol. 302 pages 340 to 342, 1983 (24 March 1983),

1.88: Hitzeman, R.A. et al., Science, Vol. 219, pages 620 to 625, 11 February 1983,

1.116: Boss, M.A. and Wood, C.R., Immunology Today, Vol. 6, No. 1, pages 12 to 13, 1985,

1.117: Wood, C.R. et al., Nature, Vol. 314, pages 446 to 449, 4 April 1985,

3.3: Declaration of Dr M.F. Tuite dated 25 May 1995,

3.4: Declaration by Dr J.M. Shulman dated 21 May 1994.

Dr Shulman's oral disclosure

IX. The Respondents I, III to VI argued essentially that:

- It was beyond dispute that Dr Shulman gave the lecture as the Mallinckrodt Award lecture as part of the 1983 Clinical Ligand Assay Society (CLAS) National Meeting on behalf of his colleague Dr Köhler who was unable to attend;

- The declarations made by Dr Shulman, and the evidence he gave before the Opposition Division in the opposition to EP 125 023 (now subject-matter of the appeal case T 1212/97), clearly established what had been made available to the public by his lecture, including the slides shown. The evidence of Dr Shulman on the slides was corroborated by the evidence of the technician who prepared them; that on the content of the lecture was confirmed by Dr Hamilton, the organiser of the 1983 CLAS meeting, who was present at the lecture and could be considered as a member of the public;

- The evidence of Dr Shulman was wholly consistent with, and thus confirmed by, the letter he wrote on January 1983 to Dr Hamilton, putting forward his intentions: *"In my presentation I propose to discuss how one might combine hybridoma system with recombinant DNA and in vitro mutagenesis techniques to generate antibodies where the variable and constant regions are precisely specified... As we discussed last month, a title could be : "Monoclonal antibodies: the prospects for serious engineering". It is a lot of material to cover..."*. Furthermore, it was wholly consistent with, and thus confirmed by, the one sheet outline of his lecture given in evidence;

- Dr Shulman had particular reasons to remember the occasion of the lecture, because unlike his colleagues he did not wish to be involved in patenting;

- The evidence put forward on behalf of the Patentees, was insufficient to outweigh Dr Shulman's clear evidence: that Dr Lyle, the only declarant who attended the lecture relied on by the Patentees, remembered the lecture only as

an overview containing nothing new, could be attributable to the lapse of time or his lack of familiarity with the subject-matter; the evidence in the form of a declaration by a paralegal as to a telephone conversation with Dr Hamilton, and exhibiting questionaries answered by others who attended the Mallinckrodt Award lecture was unsatisfactory in form and should be ignored, in particular it was unsafe as it could not be taken to reflect what those attending the lecture would have said if they had been properly questioned;

- The correct approach was for the Board to decide if the five slides relied on had been shown, and if so what a member of the public would have understood;

- As Dr Shulman was an expert lecturer, the Board should deduce what was made available to the public from a consideration of what an expert lecturer would have told his audience; also at least the contents of the letter of January 19, 1983 from Dr. Shulman to Dr. Hamilton should be treated as being made publicly available, as a sort of abstract of the lecture.

- The situation of a lecture was analogous to that of a journal accepted as having been made publicly available as of a particular date on proof of a public library having date-stamped the copy it received: it was sufficient to prove that the lecture contained the information, irrespective of whether any member of the audience actually did write down the information or understand it. If the Board had any doubts on Dr Shulman's evidence, he was available to give evidence at the oral proceedings, and should be heard.

X. Appellants I essentially argued that:

- The CLAS was an unlikely forum to choose to make a disclosure on heterogeneous Ig molecules;

- There was no mention of chimeric antibody or scheme for expressing it in Dr Shulman's letter to Dr Hamilton;

- In accordance with the case law (eg. T 890/96 of 9 September 1996), for a lecture what was made public must be established beyond reasonable doubt;

- For so fundamental a disclosure, it was remarkable that no one picked it up if it was made. In addition, the surrounding circumstances rendered it extremely unlikely that it was indeed made, namely that Dr Shulman was working on a project with collaborators and never got their consent to publication at this lecture, nor even informed them that he was going to make any disclosure relating to the collaborative work;

- If a disclosure was made at all at the lecture, Dr Shulman did not acknowledge any contribution by his collaborators: this contrasted strangely with the fact that when the work of the collaboration was expressly made public in 1984 in Nature all were expressly named. Not one of Dr Shulman's collaborators confirmed that this talk was given;

- It could not be safely concluded that Dr Shulman showed slide 534L on the expression system. There was no reliable record of anyone in audience having seen the slide or understood the subject: in fact the weight of evidence was against this, namely the declaration by Dr Lyle that he had

attended the lecture, had heard nothing new, and did not recall any mention of the matters set out in Dr Shulman's declaration and specifically relied on by Respondents I, III to VI, and the declaration by the paralegal exhibiting questionnaires completed by others who attended the lecture, which others again did not recall the lecture as providing anything not previously known;

- It was never suggested that the audience were given copies of notes or slides. No details were provided how long any slide was shown for: it may have been shown for so short a time that nobody could take note of its content;

- The evidence of Dr Hamilton was unsafe and contradictory, both in itself and in view of the evidence given by the paralegal of telephone conversation with him, to the effect that Dr Hamilton would be unable to remember anything about the 1983 CLAS meeting other than what related to the three talks he himself gave at that meeting;

Submissions regarding the substantive issues

XI. The submissions by Appellants I in writing and during oral proceedings insofar as they are relevant to the present decision are essentially the following:

Main request:

Article 83 EPC; sufficiency of disclosure

The invention was a method making use of techniques well known in the art to achieve a result that nobody else had thought of achieving but could do so once

he/she was told about said method. Thus, in 1983, the skilled person could isolate immunoglobulin (Ig) mRNA and DNA (document 1.36). In the same manner, a great deal was known about gene expression in E.coli (document 1.67), yeast (document 3.3) and mammalian cells (documents 1.61, 1.69, 1.86). Natural secretion of Igs in serum and secretion of Ig light chains from a transformed host had been observed (documents 1.40 and 1.79).

In relation to the subject-matter of claim 1 comprising the production of functional Ig molecules in mammalian cells:

- The skilled person aware from the patent specification that the method of claim 1 could be carried out in yeast would have expected that it should also be possible to carry it out in mammalian cells in general, they being more related than yeast to B lymphocytes which naturally produce antibodies.

- The patent in suit provided guidance as to which promoter and host cells to choose by making reference to documents 1.61 and 1.69. The first of these documents described the successful expression of the Ig κ light chain gene in a number of non-lymphoid cells under SV40 promoter control. Specific combinations of promoter and mammalian host cells which did not lead to expression of the Ig κ gene were also identified. The second of these documents described the transformation of an immuno-competent lymphoid cell line with the κ light chain gene under the control of its own promoter and the subsequent recovery of functional Ig. It would require no undue burden for the skilled person aware of these teachings to design a suitable system for the

expression of both the light and heavy chains in recombinant form to produce a functional Ig fragment in a single host cell.

- Appellants II and Respondents I, III to VI had not provided any evidence that the invention could not be carried out in mammalian cells.

In relation to the subject-matter of claim 1 comprising the expression of functional Ig molecules in/from bacterial cells:

The patent in suit (page 13, line 44 to page 15, line 18) provided an example of co-expression in a single bacterial cell of heavy and light Ig chains resulting in an Ig molecule being recovered in the form of inclusion bodies. Reactive material was obtained from the inclusion bodies after solubilisation and refolding (Figure 11).

First auxiliary request:

Article 83 EPC; sufficiency of disclosure in relation to the subject-matter of claims 1, 6 and 8:

- The patent in suit (page 17, line 49 to page 18, line 8) disclosed the co-expression of heavy and light Ig chains in the same yeast cells. The resulting antibody was shown to have specific antigen binding activity when directly retrieved from the yeast cells (page 18, lines 5 to 8). As the recombinant DNAs used for expression carried secretion signal sequences, said antibody would be expected also to be secreted. It was irrelevant whether high quantities of functional Igs were produced or not, since there were no requirements in the claims about the level of efficiency at which a method of production should work (see for

example, decision T 296/93, OJ EPO 1995, 625, par 4.5 of the Reasons).

- The many types of antibodies which could be produced by the claimed method were described on page 5, lines 32 to 35 of the patent in suit. The skilled reader would understand this disclosure, in particular in lines 32 to 35, as including chimeric interspecies antibodies. Appellants II and the Respondents had produced no evidence that such antibodies could not be made by the claimed process.

Article 87-88 EPC; Priority right

- A difference in disclosure between the application as filed and the priority document was that in the latter, the co-transformation of the DNA sequences encoding the light and heavy chains in the same host was not exemplified. Yet, it was a matter of routine to achieve such a transformation, taking into account the common general knowledge at the time that compatible plasmids were to be used to introduce two separate DNA sequences into the same host. This specific requirement was indeed mentioned on page 14 when discussing the co-expression of two Ig chains in E.coli.

- In the same manner, antibody secretion could be achieved without undue burden, taking into account the common general knowledge at the time.

XII. The submissions by Appellants II and Respondents I, III to VI in writing and during oral proceedings insofar as they are relevant to the present decision are the following:

Main request

Article 83 EPC; sufficiency of disclosure

In 1983, the skilled person did not expect immunoglobulin chains to be like any other proteins to be expressed by recombinant means as it was known that their synthesis in nature was strictly controlled. It was generally assumed that only B lymphocytes could produce them in stoichiometric amounts and assemble them into functional Igs (document 1.40).

In relation to the subject-matter of claim 1 comprising the production of functional Ig molecules in mammalian cells:

- The sole teaching in the patent specification with regard to carrying out the claimed process in mammalian cells was to be found on page 6, line 11 where it was stated that mammalian systems could be used for expression. The skilled person was left without any guidance on how to proceed.

- The expression of an Ig κ light chain gene in various hosts under the control of either its promoter or the SV40 promoter was described *inter alia* in documents 1.79 and 1.61. The κ promoter was found to be inactive in non-lymphoid cells and it was recognized by some but not all lymphoid cells tested. In the same manner, the expression of the κ gene from the SV40 promoter could not be obtained in all non-lymphoid cells. In all cases when expression was not achieved, many hypotheses were discussed why it should be so, leaving the skilled person in doubt as to how to proceed further. Thus, it was not a matter of routine to produce a single Ig chain in mammalian cells, let alone an immunologically functional Ig fragment.

Furthermore, the experiment described in documents 1.69 and 1.79 by which a functional Ig fragment was obtained in mammalian cells had been achieved in very specific conditions (the heavy chain being naturally synthesized by the host) and, thus, did not show how to proceed to obtain a functional Ig by recombinant means.

In relation to the subject-matter of claim 1 comprising the expression of functional Ig chains in/from bacterial cells:

The patent in suit itself provided evidence that functional Igs could not be produced in E.coli: the amount of functional Ig recovered was considered too low to do any detailed studies (page 15, line 7); the antigen-binding activity was said not to correlate with the presence of a full length Ig heavy chain (page 15, line 11). Furthermore, in the post-published document 1.116, two of the present inventors made the point that the low level of functional activity observed had never been demonstrated to be due to a protein molecule having the structure of immunoglobulin.

First auxiliary request:

Article 83 EPC, sufficiency of disclosure in relation to the subject-matter of claims 1, 6 and 8:

- The patent in suit failed to disclose adequate production of functional immunoglobulin in yeast as the specific activity of the antibody thus produced was about 0.5% as measured by ELISA (document 1.117, page 448, right-hand column). In the same manner, it did not enable secretion of a functional Ig as the heavy chain failed to be secreted when expressed alone (page 17, lines 30

to 39). Thus, there was no sufficiency of disclosure in relation to claims 1 and 6.

- Claim 8, which was directed to the production of an Ig fragment having a constant domain from a source different from that of the variable domain, comprised some embodiments such as the production of interspecies chimeric antibodies, in relation to which there was no sufficiency of disclosure.

Article 87-88 EPC: Priority right

Contrary to the application as filed, the priority document did not disclose any example of the expression of both the light and heavy Ig chains in the same yeast host cells. It, thus, failed to provide the skilled reader with the essential information that the DNA sequences encoding said chains according to claim 1 must be cloned into compatible plasmids if an Ig molecule was to be produced. In addition, secretion was also not exemplified and the production of such antibodies as chimeric interspecies antibodies which fell within the ambit of claim 8 was not mentioned.

XIII. Appellants I requested that the decision under appeal be set aside and that the patent be maintained as main request as granted and as first auxiliary request on the basis of the set of claims and description submitted as first auxiliary request on 24 May 2000 and the drawings as granted.

Appellants II requested that the decision under appeal be set aside and that the European patent No. 0 120 694 be revoked.

Respondents I, III to VI requested that the appeal of Appellants I be dismissed.

Reasons for the Decision

Dr Shulman's lecture

1. It is not in dispute that Dr Shulman gave a lecture, the Mallinckrodt Memorial lecture, at the 1983 CLAS meeting, some days before the priority date of the patent in suit, to an audience of some one hundred to two hundred persons, who would have received the information in the lecture as members of the public.

2. The question to resolve is whether there is any safe and satisfactory evidence as to the information content of what was made available to the public by the lecture, such that this information content can be taken into account when assessing novelty and inventive step. For a prior publication to take away the novelty of a claim, according to the jurisprudence of the Boards of Appeal, the subject-matter of the claim must be clearly and unambiguously disclosed in the prior publication, and also in a manner which enabled the skilled person to carry it out. For a prior publication to be relied on in assessing inventive step, it must be possible to determine the difference(s) between what was disclosed in the prior publication and what is claimed, and what hints the skilled person might have derived pointing to the claimed solution. The evidence relied on to establish the information content conveyed to the public by an ephemeral disclosure, such as a lecture, must be such that the Board is certain beyond any reasonable doubt that particular information was made available to the public. The Board cannot assess novelty and inventive step in relation to an alleged prior publication whose information content remains speculative.

3. For the evidence to be regarded as safe and satisfactory, it must unequivocally relate to what was made available to the public at the lecture. This is not a matter which this Board considers capable of being put beyond reasonable doubt by any evidence of the lecturer alone. The lecturer will have had the knowledge prior to the lecture, and will have prepared the lecture. His or her knowledge will not change as a result of the lecture, that of the audience may. The lecturer's evidence can be taken as defining the maximum amount of knowledge that may have been conveyed to the audience, but cannot be relied on to establish even what minimum of new knowledge was necessarily conveyed to the audience. The lecturer is in a quite different position to a member of the audience, and evidence of the lecturer's intentions or impression as to what was conveyed to the audience cannot even be treated as making out a prima facie case that such information was actually made available to the public, certainly as regards to information which would have been new to the audience. Here the Board's approach differs completely from that of the Opposition Division who accepted the lecturer's evidence by itself as sufficient. This approach is also the reason why the Board declined to hear Dr. Shulman at the oral proceedings before it, as further evidence from him would not serve to make up for the lack of evidence from the audience.

4. What evidence can be regarded as safely and satisfactorily establishing the information content made publicly available by a lecture will necessarily have to be judged on a case by case basis. Account must be taken of the fact that a lecture is ephemeral, so that the manner or speed of presentation may affect the comprehensibility of a lecture. Even an audio or video tape recording made of the lecture (unless themselves publicly available) would have to be treated with

caution if several hearings or viewings are necessary to extract all information. Information appearing in each of the contemporary written notes made at the lecture by at least two members of the audience can usually be regarded as sufficient, whereas information in the notes of a single member of the audience might be inadequate as reflecting the thoughts of the listener rather than solely the content of the lecture. If the lecturer read his lecture from a typescript or manuscript, or the lecturer wrote up his lecture subsequently, and the lecture was subsequently published in this form as part of the proceedings, then the written version might be taken as some evidence of the contents of the lecture, though with some caution as there would be no guarantee that a script was completely and comprehensibly read, or that a write-up was not amplified (compare decision T 890/96, supra). Most useful would be a handout given to the public at the lecture, containing a summary of the most important parts of the lecture and copies of the slides shown. None of these types of evidence are available for Dr Shulman's lecture: he did not prepare a complete script, no hand-out of the contents was made, and Dr Shulman did not write up his lecture and there was no subsequent publication of specifically this lecture.

5. Apart from the evidence of Dr Shulman, Respondents I, III to VI rely on a declaration by Dr Hamilton, who was the organiser of the 1983 CLAS meeting. Dr Hamilton did attend the lecture, but he had also as organiser corresponded and telephoned with Dr Shulman about the lecture prior to the CLAS meeting, and also at a dinner during the meeting. For this reason alone the Board finds itself unable to accept his evidence as necessarily referring to what he learnt as a member of the public attending the lecture. Secondly, his declaration, made more than a decade after the lecture, states that he has read an earlier declaration of

Dr Shulman in these proceedings. No explanation is given in his declaration as to whether anything in it relates to a recollection he had independently of reading Dr Shulman's declaration or why he feels able to recall matters with any certainty. The Board considers it relevant to be given information, why ten years after an event a witness considers he can reliably recollect what he learnt about a subject at a particular lecture, particularly where since that time he has acquired much greater familiarity with the subject. On the evidence provided the Board can only accept Dr Hamilton's evidence as confirming that nothing that Dr Shulman says is contrary to his recollections, but not as evidence of what an ordinary member of the audience at the lecture would have understood. The Board does not rely on the evidence given in form of a declaration by a paralegal concerning Dr Hamilton's memory, such hearsay evidence whilst maybe relatively easily obtainable, being inherently unsafe and unsatisfactory.

6. As there is no other evidence that supports the case of Respondents I, III to VI as to what was made publicly available at the lecture, the Board is already forced to the conclusion that there is no safe and satisfactory evidence that the information content of Dr Shulman's lecture as outlined in his declaration and exhibits thereto can be treated as having been made publicly available. Dr Shulman undoubtedly gave the lecture, but insofar as its information content went beyond what was already known in the art, or the comprehensible showing of any of the five slides specifically relied on is concerned, the Board is not satisfied on this on balance of probabilities, let alone beyond reasonable doubt.

7. In deference to the arguments of the various parties the following comments are made. For the Board it is the wrong approach to try and answer successive factual questions such as whether a slide was shown or not, and then what the audience would understand from it. The Board is concerned with the information content made available to the public. The burden of proof here is on the Respondents I, III to VI. If there is no evidence on the information content from a member of the public present at the lecture, the Board is not concerned with the precise reason why this is so. Dr Shulman himself considered that he would be covering a lot of material, and there can be no presumption that he necessarily succeeded. There is no evidence here from a technician, based on his contemporary records and stating that he operated a slide projector at the lecture, confirming that each slide particularly relied on was shown for a particular time. The only so called corroborative evidence of a technician relates to the slides being ordered in February 1983: but this is not evidence that they were actually shown.

8. The Board cannot reconstruct the information content based on any assumptions that Dr Shulman was an expert lecturer, and an expert lecturer who wished to explain the subject to an audience would have provided certain information, so Dr Shulman must have provided this information. This would be to assume the very thing which is to be proved. The circumstances of the lecture were unusual so the Board is not prepared to make any assumptions as to what happened. The lecture was not part of the ordinary 1983 CLAS meeting, but the Mallinckrodt Award Lecture. The Mallinckrodt Award had been given that year to Drs Köhler and Milstein to honour them for their work on hybridomas for producing monoclonal antibodies (work for which they later shared the 1984 Nobel prize for medicine), and Dr Shulman gave the lecture and received the award on behalf of his

colleague Dr Köhler who was prevented. Whereas it can be presumed that the audience had some acquaintance with this hybridoma work, there is no evidence that it contained anybody trying to apply genetic engineering techniques to hybridoma technology. The Board would agree with the contention of the Respondents I, III to VI that at least some members of the large audience would be expected to be able to understand. But then the absence of any evidence helpful to the case of the Respondents I, III to VI from a member of the audience is all the more surprising.

9. That Dr Shulman particularly remembered the occasion of the lecture, because unlike his colleagues he did not wish to be involved in patenting, can perhaps explain why he remembered the occasion, but is not evidence that he actually disclosed any work attributable to this collaboration in the lecture. There is no evidence that his collaborators reacted adversely to the lecture. In fact there is no evidence of anyone treating the lecture as a disclosure of something new. The printed publication of Dr Shulman and his collaborators appeared in Nature as an original publication. In the absence of conclusive evidence the Board is not prepared to find that it was in fact partly made available to the public already more than a year earlier at the lecture.

10. For the Board, the question involved here is essentially an appreciation of the evidence available in this particular case, and, thus, does not involve any important question of law such as might require a reference to the Enlarged Board of Appeal. Certainly no conflict is seen with any existing Enlarged Board Decision. The Boards of Appeal of the European Patent Office do not apply a doctrine of binding precedent, so a discussion of the numerous cases cited by the parties would serve no useful purpose as the propositions which

they establish are only of remote relevance to the present facts. The Board sees no useful analogy between evidence as to the information content of a lecture, and the situation where a journal is accepted as having been made publicly available as of a particular date on proof of a public library having date-stamped the copy it received. In the latter case there is no dispute as to information content, and the date stamp can be accepted provided there is evidence of the library's routine of date-stamping and making the journal available to the public. By contrast, there is no dispute as to the date of the lecture, but only as to its content. In the absence of evidence that any member of the audience actually did write down the information or understand it, the Board is not prepared to make any presumption as to the information content made publicly available.

11. Thus Dr Shulman's lecture insofar as Respondents I, III to VI sought to rely on it is not considered by the Board to be state of the art in the proceedings. Further, the Board cannot accede to the argument that the letter of January 19, 1983 of Dr. Shulman to Dr. Hamilton giving an outline of his proposed lecture, should itself be treated as being made available to the public. It was not written to Dr. Hamilton as a member of the public but in his capacity as organiser of the conference. Where a letter has been written to further a joint interest of the sender and the recipient, it must prima facie be treated as a private communication. Obviously here the letter was written preparatory to an intended publication of some information in the lecture. But a preparatory communication is not itself made available to the public at the time it is received, and here there is no evidence that anything in it that the Opponents might wish to rely on, was made available to the public at the lecture.

Main request

Article 83 EPC; sufficiency of disclosure

12. Claim 1 is directed in particular to the production of an immunologically functional Ig fragment in a single host cell. It, thus, has a very broad scope as it comprises production in any kind of cells including mammalian, bacterial and yeast cells. In accordance with the case law of the EPC (see, for example, T 409/91; OJ EPO 1994, 653 and T 435/91; OJ EPO 1995, 188), the skilled person has to be able to carry out the claimed process on the basis of the information given in the patent specification, over the whole area claimed, ie in all of the above mentioned cell systems, without undue burden or application of inventive skills, for the requirements of Article 83 EPC to be fulfilled.

Expression of an immunologically functional Ig fragment in mammalian cells

13. Appellants I pointed out that a process for the expression of an immunologically functional Ig fragment in mammalian cells was mentioned on page 6, lines 11 to 15 of the specification and that, in addition, prior art describing the production of a single recombinant Ig light chain in mammalian cells was described on page 4, lines 42 to 50 by reference to two documents (documents 1.61 and 1.69). They argued that common general knowledge relating to the recombinant expression of any genes in any mammalian expression systems would help putting the invention into practice and that the skilled person would consider plausible the expression in mammalian cells, as recombinant expression was successful in yeast cells.

14. The Board is not convinced that common general knowledge would have been regarded as helpful to carry out the invention in mammalian cells in view of the disclosure in document 1.69 (page 7862, left-hand column, second paragraph) that: "... *relatively little is known about the molecular mechanisms that control Ig gene expression...*". There exist "*...control mechanisms unique to lymphoid cells that allow the cells to express, assemble and secrete Igs.*" Thus, it was not expected that the recombinant expression of Ig genes in mammalian cells other than lymphoid would follow the same rules as that of other genes. As for the second one of the arguments presented, it implies that the processes for protein synthesis and protein assembly are essentially the same in yeast and mammalian cells. In the absence of any supporting evidence and taking into account that yeast and mammalian cells are phylogenetically far apart, the Board considers it as a mere assumption without proper basis.

15. Thus, the skilled person had to devise a process by which the invention could be put into practice on the basis of teachings with regard to the expression of a single Ig light chain provided in the patent in suit by way of reference to documents 1.61 and 1.69. It is also expected that he/she would be aware of the teaching of document 1.79, a document contemporaneous with document 1.69, which is equally concerned with Ig gene expression in lymphoid cells. Document 1.86 which was cited by the parties in this context does not contain any further relevant information.

16. Document 1.61 describes the expression of the gene encoding the κ Ig light chain in non-lymphoid cells under SV40 promoter control whereas documents 1.69 and 1.79 describe the expression of said gene in lymphoid cells under the control of the endogenous κ promoter. It is found that transient expression of the κ gene

occurs under SV40 promoter control in some but not all non-lymphoid cells (document 1.61, page 287, right-hand column). Continuous expression of the κ Ig light chain is obtained under the control of the κ promoter in some but not all lymphoid cells (document 1.79, abstract). These data thus provide evidence that the recombinant expression of the light chain only occurs in specific circumstances. Consequently, the claimed process which comprises said expression is not enabled for the category of mammalian cells in general.

17. Furthermore, even if it is considered that, in the light of the above mentioned documents, the patent specification discloses ways of producing Ig light chain, there remains that in order to reproduce the claimed invention, the skilled person would still be faced with solving the problems of expressing a Ig heavy chain in the same expression system as for the light chain, and of recovering functional Ig fragments therefrom, problems for which he/she would find no solution neither in the patent itself nor in the state of the art.

18. In this context, it was argued that both chains would be expected to assemble into a functional Ig fragment once they were expressed in the same host. This argument was based on the results obtained in documents 1.69 and 1.79 that a recombinant light chain expressed in a lymphoid cell which naturally produced the heavy chain could combine with said heavy chain to form an active Ig. There again, the Board notices that the experimental setting used is extremely specific, as the host cells carry a mutation which prevents the synthesis of the endogenous light chain, and the heavy chain is not synthesized in a recombinant manner. Thus,

these experiments are not indicative of whether Ig light and heavy chains would assemble correctly into a functional Ig, were they both expressed in a recombinant manner in any mammalian cells.

19. In summary, the patent specification as such provides no technical information for the production of a functional Ig fragment in mammalian cells. The state of the art which is incorporated by reference in the patent specification is silent on how to put into practice two out of three aspects of the invention (expression of the heavy chain, assembly of recombinantly produced Ig chains). With regard to the third one (expression of the light Ig chain), it provides evidence that it can only be achieved in specific circumstances. In the Board's judgment, there are, thus, serious doubts, already substantiated by prior art evidence as to whether the claimed process can be reproduced over the whole area claimed without undue burden or the exercise of inventive skills. Accordingly, a conclusion of lack of sufficient disclosure is reached even in the absence of any experimental evidence provided by Appellants II and Respondents I, III to VI that the claimed process does not work. The requirements of Article 83 EPC are not fulfilled in relation to the subject-matter of claim 1.

Expression of a functional Ig fragment in bacterial cells:

20. An experiment purportedly showing the expression of a functional Ig fragment in bacterial cells is described from page 13, line 44 to page 15, line 25 of the patent in suit. E.coli cells which are doubly transformed with DNAs encoding light and heavy Ig chains DNAs produce inclusion bodies. After solubilisation of the inclusion bodies and purification of the resulting material under conditions facilitating the formation of Ig fragments,

the presence of said fragments is tested by an assay which specifically detects the μ heavy chain in the Ig fragment (the NIP-cap-BSA assay). The results thus obtained are described in the following manner: *"The level of activity obtained in this way was **too low** to do any detailed studies on, so the resultant dialysate was purified ... This process resulted in the isolation of significant NIP-cap-BSA binding activity... This was **not found** to correlate with full length Ig μ ..."* (emphasis added by the Board). In the document 1.116 published in 1985, the present inventors discussed the nature of this NIP-cap-BSA binding activity which they and another group had observed. They stated: *" ..., a low level of functional activity (5% maximum) was recovered. Neither group demonstrated that the functional molecules formed disulphide bridges or were composed of two heavy and two light chains. However, antigen binding activity was only recovered from extracts containing both heavy and light chains. Furthermore, the refolded λμ antibodies demonstrated the same heteroclitic pattern of binding to haptens as the genuine hybridoma protein... These results are disappointing and suggest that E.coli is unlikely to prove useful for the production of functional antibodies."*. Thus, two years after the filing date of the patent in suit, the inventors themselves were still in doubt whether the activity observed in the NIP-cap-BSA binding assay could be considered as proof that functional Igs fragments had been produced in bacterial cells by the claimed process.

21. There is at best no evidence whether or not the observed activity can be attributed to the Ig fragment which E.coli synthesizes. At worst, this activity is attributed to a different molecule. It is, therefore, concluded that the teaching in the patent specification is not sufficiently clear that it can be followed to

reproduce the invention of claim 1 in a reliable manner without undue burden or exercise of inventive skills.

22. The main request is rejected because it was found that one of the claims failed to fulfill the requirements of Article 83 EPC.

First auxiliary request

23. None of the parties had any formal objections to the first auxiliary request. The Board agrees that the requirements of Article 123(2)(3) EPC and Article 84 EPC are fulfilled.

Sufficiency of disclosure

24. It was objected that the requirement for sufficiency of disclosure was not fulfilled in relation to the subject-matter of claim 1 (expression of a functional Ig fragment in yeast), claim 6 (secretion from yeast) and claim 8 insofar as chimeric interspecies antibodies fell within the scope of the claim. The Board will consider each of these points in turn.

25. The patent specification provides an example of the production of a functional Ig fragment in **yeast**: on page 16, the construction of the recombinant plasmids encoding the heavy and light chains respectively (pMA91 pre-μ and pMA91 pre-λ) is described in detail, the restriction enzymes necessary to produce the DNA fragments respectively containing the cloning vectors (based on pBR322 and the yeast 2 μ plasmid), the 5' sequence necessary for initiation of transcription and the Ig coding sequences are identified. How to retrieve from the transformed host cells and to characterize on Western blots the recombinant plasmids obtained by ligation of these fragments is explained on page 17. A

combination of E.coli-yeast shuttle vectors which is suitable to express both the μ and λ proteins in the same yeast host cells is also given on this page (lines 46 to 57). In the Board's judgment, the skilled person could reproduce these teachings without undue burden or exercise of inventive skills to produce functional Ig fragments of his/her own choice. It was objected on the basis of the post-published document 1.117 (page 448, right-hand column) that the specific activity of the antibody thus obtained was low. However, this objection is not relevant to sufficiency of disclosure because there are no requirements in the claim about the level of efficiency at which a claimed method should work (T 296/93, see supra). It is, thus, concluded that sufficiency of disclosure is met in relation to the subject-matter of claim 1.

26. In relation to the subject-matter of claim 6, it was argued that the patent in suit provided no enabling information how to achieve secretion from yeast of at least the μ heavy chain as this chain was not secreted when expressed from a DNA fragment carrying the pre-μ signal sequence for secretion. The Board notices that in the post-published document 1.117, exactly the same method is said by the present inventors to result in up to 5% or 15% of μ being found in the medium supernatant. No explanation is given for these conflicting reports, but they certainly lead to the conclusion that it is not an intrinsic feature of the μ chain that it cannot be secreted. At the priority date, sequences recognized by yeast cells as secretion signal sequences were already known in the art (see, for example, document 1.88). Thus, if the skilled person obtained a negative result with the pre-μ signal sequence, he/she would have the possibility to replace it by any other signal sequences as a matter of routine experimentation of the kind used in the patent specification for the construction of the expression

plasmids for yeast. Sufficiency of disclosure is, thus, met in relation to the subject-matter of claim 6.

27. Finally, it was objected that the patent specification was not enabling with regard to the production of chimeric interspecies antibodies, the production of which was comprised in claim 8. Yet, it is envisaged to produce such kind of antibodies on page 5, lines 32 to 35 of the patent specification and no evidence was put forward that it could not be done on the basis of the detailed teaching provided on pages 16 to 18, which teaching does not depend on the origin of the immunoglobulin DNA fragments to be expressed (see point 25, above). The objection is, thus, rejected.

28. Sufficiency of disclosure is, therefore, acknowledged.

Articles 87 and 88 EPC; Priority right

29. The disclosure in the priority document differs from that in the patent in suit in that neither the co-expression of both light and heavy chains in yeast cells nor the secretion of a functional Ig fragment are **exemplified**.

30. It was argued that this disclosure was not enabling in relation to co-expression because the information was missing that the DNAs encoding the light and heavy chains must be cloned on **compatible plasmids**. However, it is stated on page 14, lines 13 to 17 in relation with expression in E.coli: " *Another aim of this work was to express both λ and μ cDNAs in the same cell. To accomplish this requires two compatible plasmids to be present in the same cell.*" In the Board's judgment, the skilled person, at the priority date, would have understood this statement to apply to yeast as well, in the light of the fact that he/she was instructed in a

generic manner by the same disclosure to use one or two plasmids in the same host (passage bridging pages 4 and 5, page 8, lines 13 to 21). Compatible yeast vectors were readily available (see, for example, document 1.76) so that co-expression cannot be considered to involve the exercise of inventive skills.

31. Secretion is envisaged on page 9, lines 12 to 17 of the priority document. A source for the two vectors carrying the DNAs encoding the light and heavy chains together with a presequence is identified on pages 11 and 15 respectively. In the Board's judgement, the step of transforming yeast cells with said vectors is implied and evident and, so, there is neither a missing element in the claimed process (T 81/87, OJ EPO 1990, 250) nor a change of subject-matter such that it would no longer be the same invention as required for validly claiming a right to priority under Article 87(1) EPC (cf. decision of the Enlarged Board of Appeal G 2/98 to be published in the Official Journal of the EPO). Sequences recognized by yeast cells as secretion signal sequences were already known in the art at the priority date, (see, for example, document 1.88). If confronted with the problem that anyone of the Ig chains was not secreted, the skilled person could replace the secretion sequence with anyone of these other secretion sequences using such routine method as described in the priority document (pages 11 to 18) for the construction of recombinant plasmids.

32. For these reasons, priority is acknowledged.

Articles 54 and 56 EPC; novelty and inventive step

33. Once the Board had given its decision on what the lecture by Dr. Shulman made available to the public, no objections were raised against the novelty or inventive step of this request. The Board also agrees that there

are no documents on file prejudicial to the claim request under the provisions of Articles 54 EPC and 56 EPC, taking into account that in view of the above findings, the patent enjoys as filing date that of the priority document (Article 89 EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the set of claims and description submitted as first auxiliary request on 24 May 2000 and the drawings as granted.

The Registrar: The Chairwoman:

U. Bultmann U. Kinkeldey