BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

Datasheet for the decision of 19 July 2006

Case Number: T 0956/03 - 3.3.08

Application Number: 96940448.2

Publication Number: 0866967

IPC: G01N 33/50

Language of the proceedings: EN

Title of invention:
Use of nuclear magnetic resonance to identify ligands to target biomolecules

Patentee:
ABBOTT LABORATORIES

Opponents:
Sanofi-Aventis Deutschland GmbH
Bayer AG
Boehringer Ingelheim Pharma GmbH & Co. KG
F. HOFFMANN-LA ROCHE & CO.
Pfizer Health AB
Combinature Biopharm AG

Headword:
NMR/ABBOTT LABORATORIES

Relevant legal provisions:
EPC Art. 54, 56, 108, 123(2)(3)

Keyword:
"Restitutio in integrum (yes)"
"Transfer of right to appeal against decision in opposition proceedings: only acknowledged when evidence of transfer filed"
"Main request (claims 1 to 4 as granted) - novelty (yes)"
"Inventive step (yes)"

Decisions cited:
G 0002/88, G 0004/88, G 0002/04, T 0195/84, T 0475/88, T 0563/89, T 0659/92, T 0870/92, T 0670/95, T 0298/97, T 1137/97, T 0656/98, T 0074/00, T 0413/02, T 1091/02, T 0261/03

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0956/03 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 19 July 2006

Appellant I: (Patent Proprietor)
ABBOTT LABORATORIES
Chad 0377/AP6D-2
100 Abbott Park Road
Abbott Park
Illinois 60064-3500 (US)

Representative:
Modiano, Micaela Nadia
Modiano, Josif, Pisanty & Staub Ltd.
Baaderstrasse 3
D-80469 München (DE)

Appellant II: (Opponent 03)
Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
D-88397 Biberach an der Riss (DE)

Representative:
-

Appellant III: (Opponent 01)
Sanofi-Aventis Deutschland GmbH
Industriepark Höchst K 801
D-65926 Frankfurt am Main (DE)

Representative:
Ackermann, Joachim
Postfach 11 13 26
D-60048 Frankfurt am Main (DE)

Respondents: (Opponent 02)
Bayer AG
Konzernbereich RP
Patente und Lizenzen
D-51368 Leverkusen (DE)

Representative:
-

(Opponent 05) F. HOFFMANN-LA ROCHE & CO.
Aktiengesellschaft
Grenzacherstrasse 124
CH-4002 Basel (CH)

Representative: Vossius & Partner
Siebertstrasse 4
D-81675 München (DE)

(Opponent 06) Pfizer Health AB
Patent Department
S-112 87 Stockholm (SE)

Representative: -

Other Party:
(Opponent 07) Combinature Biopharm AG
Robert Rössle Strasse 10
D-13125 Berlin (DE)

Representative: Jungblut, Bernhard Jakob
Albrecht, Lüke & Jungblut
Patentanwälte
Gelfertstrasse 56
D-14195 Berlin (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 7 July 2003 concerning maintenance of the European patent No. 0866967 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
C. Rennie-Smith

Summary of Facts and Submissions

I. The appeals lie from the interlocutory decision of the opposition division posted on 7 July 2003 concerning the European patent No. 0 866 967 with the title "Use of nuclear magnetic resonance to identify ligands to target biomolecules". The patent, which was based on application No. 96 940 448.2 (published as WO 97/18471), was granted with seven claims.

II. Claim 1 as granted read as follows:

"1. A process of screening compounds to identify compounds that are ligands that bind to a specific target molecule comprising the steps of:

a) generating a first two-dimensional $^{15}N/^{1}H$ NMR correlation spectrum of a ^{15}N-labeled target molecule;

b) exposing the labeled target molecule to one or a mixture of chemical compounds;

c) generating a second two-dimensional $^{15}N/^{l}H$ NMR correlation spectrum of the labeled target molecule that has been exposed to one or a mixture of compounds in step (b); and

d) comparing said first and second two-dimensional $^{15}N/^{l}H$ NMR correlation spectra to determine differences between said first and said second spectra, the differences identifying the presence of one or more compounds that are ligands which have bound to the target molecule."

Dependent claims 2 to 4 concerned different embodiments of the process of claim 1. Independent claim 5 and dependent claims 6 and 7 related to processes of

determining the dissociation constant between a target molecule and a ligand that binds to that target molecule.

III. The patent was opposed by seven parties on the grounds of Article 100(a) and (b) EPC, in particular lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC) and lack of sufficient disclosure (Article 83 EPC). Opponent 04 withdrew its opposition during opposition proceedings.

IV. The opposition division found that, whereas the main request (claims 1 to 4 as granted) was not allowable due to lack of novelty of the subject-matter of claim 1, the first auxiliary request filed at the oral proceedings fulfilled the requirements of the EPC. Thus, in an interlocutory decision pursuant to Article 102(3) EPC the patent was maintained on the basis of the first auxiliary request and a description amended accordingly.

V. The proprietor of the patent, opponents 03 and 07, and Aventis Pharma Deutschland GmbH, which claimed to be successor in law to opponent 01, each filed a notice of appeal against the interlocutory decision of the opposition division. Aventis Pharma Deutschland GmbH said in its notice of appeal that a copy of the document transferring the rights of opponent 01 to it would be filed later. Each of those parties also paid an appeal fee in due time except for the patent proprietor. On 15 September 2003, the patent proprietor filed an unsigned cheque for the appeal fee which was returned and re-filed after signature on 19 September 2003. By its letter dated 29 October 2003, the

proprietor requested *restitutio in integrum* under Article 122 EPC and paid the appropriate fee for such a request.

VI. Opponent 07 withdrew its opposition on 4 November 2003. The patent proprietor (appellant I), opponent 03 (appellant II) and Aventis Pharma Deutschland GmbH (appellant III) each filed a statement setting out the grounds of appeal within the time limit set in Article 108 EPC. In the event that the board decided not to allow their respective requests, oral proceedings were requested by each of the appellants. Aventis Pharma Deutschland GmbH (appellant III) did not file the transfer of rights document referred to in its notice of appeal with its statement of grounds of appeal filed on 17 November 2003 although it did, in a separate letter of that date, refer again to its succession to the rights of opponent 01 in withdrawing previous authorisations given to representatives of that opponent.

VII. In a communication sent on 10 December 2003, the board expressed its provisional opinion on the request for *restitutio* by the patent proprietor - which it considered to be *prima facie* admissible and allowable - as well as on the admissibility of the appeal by appellant III - which it considered with reference to decision T 1137/97 (of 14 October 2002, unpublished in OJ EPO) might be inadmissible in the absence of evidence to support the claim that appellant III was the successor in law to opponent 01. The parties were invited to file submissions on these issues.

VIII. In response to the board's communication, appellant III filed written arguments of 5 February 2004 and accompanying evidence in support of its claim to be the universal successor in law of opponent 01. No written submission dealing with the procedural issues raised in the communication was received from the other parties, but appellant I submitted observations on the statements of grounds of appeal filed by the other appellants.

IX. The parties were summoned to oral proceedings. In a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal attached to the summons, the board drew attention to matters to be discussed at oral proceedings, in particular to issues in connection with Articles 54 and 56 EPC.

X. In a letter received on 30 March 2006, appellant III informed the board that its name had changed to Sanofi-Aventis Deutschland GmbH, for which evidence was provided.

XI. In response to the board's communication, appellant I filed on 19 June 2006 three additional auxiliary requests (auxiliary requests 2 to 4) together with new documentary evidence. The main request (claims 1 to 4 as granted) and the auxiliary request considered by the opposition division were maintained as main request and auxiliary request 1, respectively.

XII. Oral proceedings were held on 19 July 2006 in the presence of the appellants, none of the respondents and the other party being present although duly invited. In the course of the proceedings, appellant I submitted in

writing its own definition of the term "screening" in claim 1 as granted. The definition read:

"*screening is random testing of synthetic chemical and natural databases (libraries) to discover compounds that bind to a particular target molecule and serve as new drug leads, such libraries having been constructed or acquired with no prior knowledge of those compounds that are already known to bind to the particular target molecule.*"

XIII. The following documents will be referred to in the present decision:

D4: T. Ohkubo et al., J. Biochem., Vol. 110, pages 1022 to 1029, 1991;

D5: H. Baumann et al., J. Mol. Biol., Vol. 247, pages 840 to 846, 1995;

D12: V. Ramesh et al., Eur. J. Biochem., Vol. 225, pages 601 to 608, 1994;

D15: Y. Oda et al., Journal of Biomolecular NMR, Vol. 1, pages 247 to 255, 1991;

D22: G. Otting, Current Opinion in Structural Biology, Vol. 3, pages 760 to 768, 1993;

D26: X. Cheng et al., J. Am. Chem. Soc., Vol. 117, No. 34, pages 8859 to 8860, 1995;

D33: T. Thewes et al., The Journal of Biological Chemistry, Vol. 265, No. 7, pages 3906 to 3915, 5 March 1990;

D68: M.R. Rejanic et al., Biochemistry, Vol. 30, pages 11081 to 11092, 1991;

AVED1: K.S. Koblan et al., Protein Science, Vol. 4, pages 681 to 688, 1995;

D78: L.P. Schacter et al., Seminars in Oncology, Vol. 19, No. 6, pages 613 to 621, December 1992.

XIV. The arguments put forward by appellant I can be summarized as follows:

Restitutio in integrum

The appellant supplied a cheque for the appeal fee to the EPO on 15 September 2003, before the final date for payment of 17 September 2003. By oversight the cheque had not been signed. It was returned to the appellant's representative and re-filed, having been signed, on 19 September 2003. The omitted act had thus been performed as soon as its omission was known to the appellant, it was an isolated omission in an otherwise well-organised office, and accordingly *restitutio* should be allowed.

Novelty in view of D4, D5 or D12

Claim 1 provided a process for methodically examining compounds in order to make a separation into different groups, namely the group of compounds that bound to the

target molecule (which were "selected" through the screening process) and the group of compounds that did not bind to the target molecule (which were "eliminated" through the screening process). Screening meant "separation by selection" and entailed testing more than one potential ligand. If only one compound known to bind to the target molecule was tested, the test could not be considered as a screening process.

None of the documents on file disclosed a screening process as claimed. Document D4 related to the identification of substrate binding sites of human lysozyme. In this document the interaction between the lysozyme and its inhibitor N-acetyl-chitotriose was investigated using ^{15}N-^{1}H NMR spectra. Since N-acetyl-chitotriose was known to be a ligand of human lysozyme, D4 did not disclose a screening process. In document D5 nuclear magnetic resonance (^{15}N-^{1}H spectra) was used to identify the DNA-binding surface of the Sso7d protein from *Sulfolobus solfataricus*. For this purpose binding of two different DNA oligomers to the protein was investigated; this could, however, not be equated to carrying out a screening process within the meaning of the patent because no or limited sequence specificity was expected for the Sso7d protein that was known to bind double-stranded DNA in a non-specific manner. In document D12 the results of a spectroscopic study on the effects of the binding of the corepressor L-tryptophan and an operator oligonucleotide to *E. coli trp* repressor were reported. Since the two ligands were known, the purpose of the study was not to screen for new ligands, but rather to characterise the *trp* repressor-tryptophan and *trp* repressor-tryptophan-oligonucleotide complexes.

Inventive step

Documents D33 and D68 concerned the use of one-dimensional NMR spectroscopy for characterizing the binding of various lysine analogs to either the kringle-4 or kringle-5 domains of human plasminogen. Neither document disclosed or suggested the use of NMR spectroscopy for screening compounds to identify compounds that are ligands for a specific target molecule. All compounds tested in D33 and D68 were known ligands or were chosen specifically in the serious expectation that they would bind to a greater or lesser extent to the target molecule. Characterizing the binding affinity of a target molecule with respect to its known ligand (or to structurally analogous derivatives thereof) did not qualify as a method of screening compounds in order to identify those, if any, which actually bound to a target molecule.

In document AVED1, NMR was used as a tool for designing nonpeptidal inhibitors of the farnesyl-protein transferase that were selective, potent and exhibited appropriate pharmacological properties. Designing a drug was, however, different from screening for a potential drug. The experiments reported in D5 aimed at identifying the DNA-binding surface of the Sso7d protein using NMR as known in the prior art.

D26 suggested the possibility of using ESI mass spectrometry for screening libraries for tight-binding compounds, but there was no motivation for the skilled person to replace mass spectrometry by a different method, let alone by NMR.

Document D22 was a review on NMR as a tool with which to study protein-ligand interactions. No hint was given either in this document or in document D12 that would prompt the skilled person to apply this technique to screening for new ligands of a given molecule.

XV. The arguments submitted by appellant II, as far as they are relevant to this decision, were essentially as follows:

Novelty in view of D4, D5 or D12

All four steps of the claimed process were described in the prior art documents D4, D5 and D12. The alleged distinguishing feature "screening compounds" in claim 1 was equivalent to "screening a compound" and, therefore, the number of compounds tested by ^{15}N-^{1}H NMR was not relevant to the assessment of novelty. The purpose of the experiments described in the prior art documents was to determine whether or not the ligand bound to the target protein. The fact that the tested compounds were known to be ligands of the protein was irrelevant in the framework of assessing novelty, as the claims did not require that the tested compounds were totally unknown or, at least, not known to be ligands.

Inventive step

Document D33 represented the closest prior art. In this document a series of compounds was tested as potential ligands to the kringle 5 domain of plasminogen by comparing the ^{1}H or ^{1}H-^{1}H spectra of the protein before and after addition of the tested compound. The

technical problem to be solved in view of D33 was to provide an alternative or improved screening process to identify ligands of a given molecule. The solution provided in the patent, ie the use of two-dimensional ^{15}N-^{1}H NMR to identify ligands to a target molecule, was obvious in view of the disclosure of document D12 which described the characterization of ligand-target complexes by monitoring changes in the target molecule upon binding of a ligand by comparison of the ^{15}N-^{1}H NMR spectra. The advantages of the ^{15}N-^{1}H NMR method, namely a better resolution and the possibility to test more than one ligand at once, were specifically mentioned on page 604, left column, first full paragraph. These and other advantages were apparent also from document D22 (cf. paragraph bridging pages 764 and 765). Since the insufficient resolution of ^{1}H-^{1}H NMR spectra was mentioned as a drawback in document D33 (cf. page 3912, right column, footnote 2), the skilled person would have a motivation for using ^{15}N-^{1}H NMR spectra to screen for new ligands.

Alternatively, document D26 could be considered as the closest prior art. In this document electrospray ionization mass spectrometry was said to be useful in screening libraries of compounds for tight-binding compounds. In view of the advantages of ^{15}N-^{1}H NMR mentioned in document D12 and the high costs of mass spectrometry, the skilled person would have had a motivation for replacing the method used in D26 by the method disclosed in documents D4, D12 or D15, thus arriving at the screening process claimed in the patent.

XVI. The arguments put forward by appellant III can be summarized as follows:

Admissibility of its appeal

The facts in decision T 1137/97 referred to in the board's communication of 10 December 2003 (see paragraph VII *supra*) were different from those of the present case. T 1137/97 concerned the transfer of assets between companies whereas this case concerned the universal succession by one company to all the rights and interest of another. In the earlier case it was not clear by the end of the time for filing an appeal who the appellant was: in the present case, the appeal was filed in the name of the universal successor.

Other case-law of the Boards of Appeal supported the appellant's position. In G 4/88 (OJ EPO 1989, 480) the Enlarged Board of Appeal held that an opposition could be transferred together with, and inseparable from, all the assets of a business. In such circumstances a transferee could be acknowledged as a party and no time limit was set for filing evidence of the transfer.

In T 563/89 (of 3 September 1991, unpublished in OJ EPO), the appellant explained in its notice of appeal that it had succeeded to the rights of the opponent by acquiring the opponent company. Evidence in the form of the acquisition agreement was filed after the expiry of the time for appealing. The parties knew the identity of the appellant from the beginning of the appeal proceedings and no time for filing evidence of the transfer was set.

Decision T 656/98 (OJ EPO 2003, 385), which concerned the position of patent proprietors, held that for a transferee of a patent to appeal the necessary documents establishing the transfer, the transfer application and transfer fee must be filed before expiry of the appeal period (see the headnote). However, different conditions applied to opponents and the appellant cited paragraph 4.3:

> "By decision G 4/88 (supra) assignments of oppositions are only possible in restricted circumstances: that different conditions are imposed on opponents and patentees when assigning their status as parties does not seem to amount to any sort of unjustifiable discrimination. Patents can be assigned much more freely than oppositions, subject only to the formalities of Rule 20 EPC being complied with." (Emphasis added by the appellant.)

The appellant filed documents with its submissions of 5 February 2004 evidencing its position as successor to opponent 01. A request to acknowledge the transfer was to be implied in its notice of appeal. It concluded from the above arguments and those documents that the end of the appeal period (in this case 17 September 2003) should not be the latest date for filing evidence of the transfer of an opposition and that its appeal should be held admissible.

Novelty in view of D4

Since each step of the claimed process was described in document D4, the assessment of novelty revolved around

the interpretation of the term "screening". The narrow definition of this term given by the proprietor did not correspond to the meaning conveyed by the description of the patent, in which reference was made to "putative ligands" and "compounds suspected of being ligands". Furthermore, having regard to claim 2 that was directed to a process for confirming the ability of a compound to function as a ligand, the subject-matter of claim 1 would also encompass testing potential ligands previously found by a screening method not based on ^{15}N-^{1}H NMR.

Inventive step

The closest prior art was document D5, in which ^{15}N-^{1}H nuclear magnetic resonance was used to identify the DNA-binding surface of the Sso7d protein from *Sulfolobus solfataricus*. For this purpose, two different DNA oligomers that bound to the protein were tested. The addition of the DNA resulted in very specific changes in the two-dimensional NMR spectrum which allowed to determine whether or not the DNA molecule was bound to the protein. Thus, in view of the disclosure of D5 alone a screening process as claimed was obvious to the skilled person.

Alternatively, document D68 could serve as starting point for the assessment of inventive step. D68 described the screening of different compounds varying in size, aromatic/aliphatic character, and ionic charge distribution for their ability to bind to plasminogen, the screening being based on the ^{1}H NMR spectra before and after addition of the tested compound to plasminogen. Moreover, D68 suggested that the

information obtained from ^{1}H NMR spectra could assist in assessing potential ligands for plasminogen as antifibrinolytic drugs (cf. page 11082, left column, last full paragraph). Since the sole difference between the teaching of D68 and the process of claim 1 was the use of a different NMR method, namely ^{15}N-^{1}H NMR, and this was already suggested in document D22, the claimed process did not involve an inventive step.

A further starting point for the assessment of inventive step could be document AVED1. Figure 3 of this document illustrated the results from a ligand competition experiment, in which binding of a tetrapeptide inhibitor (CVWM) and a novel pseudopeptide inhibitor (L-739,787) to farnesyl-protein transferase were assessed by two-dimensional NMR spectroscopy.

XVII. Appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained with claims 1 to 4 as granted, or, as auxiliary request 1, that the appeals of opponents 01 and 03 be dismissed, or, as auxiliary requests 2 to 4, that the decision under appeal be set aside and the patent be maintained on the basis of any of auxiliary requests 2 to 4 as filed on 19 June 2006.

Appellants II and III (opponents 03 and 01 respectively) requested that the decision under appeal be set aside and that the European patent be revoked.

Reasons for the Decision

Request of appellant I for restitutio in integrum

1. On the evidence it is perfectly clear that the patent proprietor's representative took all necessary steps to file an appeal in due time except that she overlooked the signature of the cheque by which the appeal fee was to be paid. The cheque was however prepared and filed in due time together with the notice of appeal but the absence of a signature meant that payment of the fee could not be completed in time. The cheque was returned to and promptly signed and re-filed by the representative on 19 September 2003. The appellant thus rectified the omitted act as soon as the omission became apparent. It can easily be imagined that in even the best-ordered offices a cheque may occasionally be enclosed unsigned with other documents. None of the other parties made any submissions at all on this issue, let alone any submissions opposing the *restitutio* request, despite being invited by the Board to file observations if they wished (see Section VII *supra*). Accordingly, the Board considers it appropriate to allow the request.

Admissibility of the appeal by appellant III

2. It is well-established that oppositions, while they may not be freely transferred, can be transferred in certain circumstances - from one natural or legal person to another together either with those assets of a business in the interest of which the opposition was commenced or by universal succession to all assets, as for example by merger; and from a deceased person to

his or her heir or heirs (see G 4/88 OJ EPO 1989, 480; G 2/04 OJ EPO 2005, 549; T 475/88 of 23 November 1989; T 74/00 of 15 March 2005). Such transfers may be allowed not just of pending oppositions but also of the right to appeal following opposition proceedings and of opposition appeals (see T 563/89 of 3 September 1991, Reasons, paragraph 1.1; T 659/92 OJ EPO 1995, 519, Reasons, paragraphs 1 to 3; T 74/00, Reasons, paragraph 5). It is also well-established that, in order for a transferee to be acknowledged in place of an original opponent, appropriate evidence must be produced to satisfy the Opposition Division or Board of Appeal that an allowable transfer has occurred (see T 659/92 *ibid*, Reasons, paragraphs 1 to 3; T 298/97 OJ EPO 2002, 83, Reasons, paragraph 7.2; T 74/00, Reasons, paragraph 4; T 261/03 of 24 November 2005, Reasons, paragraph 3.5). In the absence of such evidence, a request to acknowledge a transfer will be refused (see T 659/92 *ibid*, Reasons, paragraph 3.3; T 74/00, Reasons, paragraphs 9 to 14).

3. The only question, on the answer to which the admissibility of appellants III's appeal depends, is "when must such evidence be filed?" If the necessary evidence must be produced before a transfer is acknowledged then, in cases such as the present where the transfer occurs before an appeal is filed, the effective deadline for filing the evidence is the expiry of the appeal period. The issue is highlighted in the present case since appellant III otherwise did everything necessary to file an admissible appeal by a transferee. It filed a notice of appeal in time under Article 108 EPC. It made a request to be acknowledged as transferee - not an explicit request but the Board

accepts the reference to a change of party as an implicit request as the appellant subsequently submitted (and as was similarly held in T 261/03 of 24 November 2005, Reasons, paragraph 3.3). It explained the reason for the request, namely that it was the successor in law to opponent 1, and the evidence when filed showed perfectly credibly that such was the case. No other party questioned the evidence and, the time of filing apart, the transfer would almost certainly have been acknowledged without question.

4. The jurisprudence of the Boards of Appeal clearly suggests that a transfer can only be acknowledged as from the date when adequate evidence is produced (see T 870/92 of 8 August 1997, Reasons, paragraph 2; T 670/95 of 9 June 1998, Reasons, paragraph 2; T 1137/97 of 14 October 2002, Reasons, paragraph 4; T 413/02 of 5 May 2004, Reasons, paragraph 3; and T 261/03 of 24 November 2005, Reasons, paragraph 3.5.1). This is consistent with the principle that a patent proprietor and, as the case may be, the Opposition Division or the Board of Appeal should know the identity of the party opposing a patent (see T 1137/97, Reasons, paragraph 4; T 74/00, Reasons, paragraph 7; and generally "Case Law of the Boards of Appeal of the European Patent Office", 4th Edition, pages 465 to 466, section VII.C.8.3.2). However, it was remarked in T 261/03 (Reasons, paragraph 3.5.1), that some doubts remain and that these were summarised in T 1091/02 (OJ EPO 2005, 14) at paragraph 3.3 of the Reasons. In fact, that paragraph of that decision cites other decisions of the Boards of Appeal which support the view that the effective date of a transfer is the date on which adequate evidence is provided (T 1137/97, T 870/92 and

T 670/95), refers to the reason for that view being certainty as to the identity of parties (see T 1137/97, Reasons, paragraph 4), and then gives examples of two cases where later-filed evidence was said to have been acceptable. This appears to have happened in the first case, T 563/89 of 3 September 1991, but the relevance of that decision is the extension of the principle of G 4/88 from pending oppositions to the right to appeal against opposition decisions. In the second case, T 298/97 (OJ EPO 2002, 83), when the Board itself at a late stage of the case observed an apparent discrepancy not seen by the parties, it directed evidence to be filed in order to establish what had actually happened. In fact, neither decision indicates at all that the time by when evidence of a transfer should be filed was considered as a question as such.

5. Appellant III argued, first, that the present case differs from a number of those previously decided and, second, that different considerations apply to the transfer of oppositions than to the transfer of patents. As regards the three cases cited in support of the first argument, the Board has commented above on T 563/89 (see point 4) in which apparently the evidence was filed after the existence of the transfer was made known. The appellant observes that in that case no time for filing evidence was set. It is true no mention is made of any such time limit and it appears the point was simply not considered. Nor was it apparently considered by the Enlarged Board of Appeal in G 4/88 (*supra*) to which the appellant refers as another example of a case where no time limit was set. One would not of course expect the Enlarged Board, which quite clearly limited its opinion to the question

before it as to the possibility of a transfer of opposition in certain specific circumstances (see Reasons, paragraph 5), to volunteer an opinion on additional points not referred to it. Indeed, even in the later Enlarged Board case G 2/04 (OJ EPO 2005, 549), when the question of the time limit was raised by the referral case (T 1091/02, OJ EPO 2005, 14, Reasons, paragraph 3 and Order, Question 2), it was not answered in view of the negative answer given to a preceding question (see G 2/04, Reasons, paragraph 3).

6. The third case referred to by appellant III is T 1137/97 of 14 October 2002, which was also referred to by the Board in its communication. The appellant submitted that the facts of that case were different from those of the present: T 1137/97 concerned the transfer of assets between companies whereas this case concerned the universal succession by one company to all the rights and interest of another. In the earlier case it was not clear by the end of the time for filing an appeal who the appellant was: in the present case, the appeal was filed in the name of the universal successor. The Board has, after careful consideration of that distinction, come to the conclusion that the type of transfer should make no difference to the time when evidence of a transfer must be filed. It is indeed true that in T 1137/97 the position was not entirely clear by the end of the time for filing an appeal - and it was in order to avoid such lack of clarity that Board 3.3.4 made the following observations in that case which are entirely apposite to all transfers of oppositions:

"*4. For the purpose of EPO proceedings, the effective date of the transfer of an opposition must be taken as the date when the transfer has been requested at the EPO and adequate evidence provided.... As an opponent is not required to have any interest to file an opposition, a transfer of an opposition is something that has to be requested at the EPO together with supporting evidence before it can take effect. This is also conducive to procedural certainty as to who are the appropriate parties.*"

In all cases of transfers of oppositions, evidence must be produced since otherwise any party could purport to be a successor to an original opponent. Contrary to appellant III's arguments, the Board considers it would be both illogical and undesirable to allow one category of purported successors more time to file such evidence than another. Legal certainty requires that the identity of a party, including a replacement party, be established beyond doubt as soon as possible and that principle cannot be allowed to vary according to the type of transfer or the facts peculiar to one case. If, as appellant III has argued, it was clear when the appeal was filed who the filing party was, then it should have been possible at that time also to file evidence to that effect.

7. Appellant III's second argument, that different considerations apply to the transfer of oppositions than to the transfer of patents, was founded on the decision in T 656/98 (*supra*) which held that, for a transferee of a patent to appeal, the necessary transfer documents, application and fee must be filed before the expiry of the appeal period. While the

passage from T 656/98 cited by the appellant (cf. Reasons, paragraph 4.3, see Section XVI *supra*) makes the general statement

"different conditions are imposed on opponents and patentees when assigning their status as parties"

this cannot *per se* mean, as appellant III must infer it means, that it is not necessary to file evidence to support the transfer of an opposition before the transfer can be acknowledged. Indeed, the same passage states clearly that the transfer of oppositions is more restricted and the transfer of patents more free.

7. In the present Board's view, the case-law shows a definite balance in favour of the view that a transfer can only be acknowledged from, at the earliest, the date when adequate evidence to prove the transfer has been filed. This is desirable in the interest of legal certainty and, within that principle, to ensure the identity of an opposing party is known. If the transfer takes place before the appeal period expires then the entitlement of the transferee to replace the opponent must be established by filing the necessary evidence before the appeal period expires. Accordingly, since that was not done in the present case, the appeal of appellant III is inadmissible.

Novelty (Article 54 EPC) - Claims 1 to 4 as granted

8. In the decision subject to appeal, the opposition division found that the subject-matter of claim 1 as granted lacked novelty in view of document D4. On

appeal, novelty has been disputed also with regard to documents D5 and D12.

Document D4

9. In the view of the opposition division, claim 1 included the option of carrying out the screening process by exposing the target molecule to a single compound, so that said compound could be identified as a ligand for the target molecule. Since in the method disclosed in D4 also one compound was identified as a ligand to a given target molecule, all features of one of the embodiments encompassed by claim 1 were considered to be anticipated by D4. Consequently, the subject-matter of claim 1 was found to lack novelty in view of this document.

10. In the board's view, this finding, which has been contested by appellant I (see Section XIV, *supra*), cannot bear close examination. Document D4 reports a series of NMR studies on human lysozyme with the aim of investigating the structural and functional aspects of this enzyme in solution (cf. page 1022, left column, last three lines of the first paragraph). In an initial experiment, all of the backbone ^{15}N signals in uniformly ^{15}N labelled lysozyme were assigned on the basis of the analysis of ^{1}H and ^{15}N NMR spectra, particular attention being focussed on the signals for the side chain NH_2 groups of asparagine and glutamine side chain amides (cf. Figures 1 and 4; page 1027, left column, second paragraph to page 1028, right column, second full paragraph).

11. In a further experiment, the information obtained from the ^{15}N-^{1}H spectra was applied to the study of the binding interactions between human lysozyme and its well-known inhibitor N-acetyl-chitotriose ($(GlcNAc)_3$). Upon titration with increasing $(GlcNAc)_3$ concentrations, many NH proton signals changed in chemical shifts or decreased in intensity. The different behaviours of the signals were postulated to reflect chemical shift differences between free and $(GlcNAc)_3$ bound forms of the lysozyme.

12. The board acknowledges that – as the opposition division asserted in its decision - each of the four individual steps a) to d) of one of the two embodiments of the process defined in claim 1, namely the embodiment involving exposure of the labelled target molecule to one chemical compound (cf. paragraph II *supra*) can be inferred from document D4. However, the board is unable to find in this document a clear and unambiguous disclosure of a **screening** method for **identifying** compounds which function as ligands of the protein in question. This is an essential technical feature of the claimed process, as it defines the purpose of carrying out the method and the technical effect to be achieved (cf. G 2/88, OJ EPO 1990, 93 for product claims).

13. The patent as granted does not include a definition of the term "screening" used in claim 1. Thus, for the purpose of interpreting the claim in the framework of assessing novelty, the term "screening" has to be construed as it was generally understood in the art at the priority date. As it is apparent from document D78 (cf. page 615, left column, first paragraph under the

heading "Screening"), in the field of drug discovery and development, in which the claimed invention lies, a screening process is understood as a series of tests that aim at the evaluation of a number of compounds in order to distinguish compounds having a particular feature from those lacking the feature in question. These tests can be carried out either for each compound individually or for a mixture of compounds which, in one or several further steps, is resolved into its individual components.

14. In claim 1 as granted, the compounds screened for are defined by their ability to bind to a specific target molecule. Thus, the decisive question in the context of novelty over the disclosure of document D4 is whether or not this document describes a **series** of tests that aim at **distinguishing** between compounds which bind to human lysozyme and those which do not. This question must be answered in the negative.

15. Whereas it is true that in the experiments described in document D4 the ability of $(GlcNAc)_3$ (the ligand) to bind to human lysozyme (the target protein) is tested, the expressed aim of the study of D4 is the **identification and characterization of the binding sites** in the lysozyme protein (cf., *inter alia*, page 1022, right column, last sentence of the second full paragraph; and page 1027, left column, first sentence of the second paragraph). In other words, the purpose of the experiments described in D4 is neither to determine whether or not $(GlcNAc)_3$ binds to lysozyme, since this was admittedly well-known in the art, nor to distinguish between compounds that - as $(GlcNAc)_3$ - bind to lysozyme and those which do not. Rather, the object

of the exercise was to find out at which position and in which manner $(GlcNAc)_3$ binds to lysozyme. This is apparent from a number of statements in D4, and in particular from two passages cited by appellant II itself, namely lines 12 to 13 of the Abstract ("*The interaction between human lysozyme and its inhibitor N-acetyl-chitotriose was investigated by ^{15}N-^{1}H HMQC spectra*") and the passage on page 1028, right column, third full paragraph, lines 13 to 15 ("*The modes of binding of N-acetyl-chitotriose $(GlcNAc)_3$ were examined by means of a ^{15}N-^{1}H HMQC experiment.*").

16. It follows from the above that an essential technical feature of the process of claim 1, namely the purpose of carrying out the process and the technical effect achieved ("*to identify compounds that are ligands that bind to a specific target molecule*") is not clearly and unambiguously disclosed in document D4. Thus, document D4 cannot be considered to make available to the public a **screening** method as claimed. Consequently, contrary to the findings of the opposition division in the decision under appeal, the subject-matter of claim 1 is considered to be novel over the disclosure of document D4.

Document D5

17. On appeal, appellant II based a further novelty objection on the disclosure of document D5. This document describes the characterization of the DNA-binding surface of the Sso7d protein, a protein of *Sulfolobus solfataricus* which binds strongly to double-stranded DNA homopolymers, using two-dimensional ^{15}N-^{1}H NMR spectroscopy (see Abstract). The identification of

the binding site was based on changes in the ^{15}N-^{1}H NMR correlation spectrum of ^{15}N-enriched Sso7d upon complexation with a ten base-pair DNA duplex or a 19 base-pair DNA duplex. The DNA oligomers used in the study were chosen based on availability only, but their sequence was less important for the Sso7d protein, for which no or only a limited sequence specificity could be expected (cf. page 841, right column, first paragraph under the heading "The n.m.r. spectrum of Sso7d-DNA complexes in rapid exchange"). Based on the data obtained from the spectra and on previous evidence, a model of the non-specific Sso7d-DNA complex was suggested (see page 844, under the heading "Model of the Sso7d-DNA complex").

18. As for document D4, the board is unable to find in document D5 a clear and unambiguous disclosure of a **screening** method. Contrary to appellant II's view, the fact that two different DNA oligomers are used as ligands in the experiments described in document D5 does not necessarily amount to the disclosure of a screening method. It is not solely the plurality of compounds tested that characterizes a method of screening, but the purpose to be accomplished, namely to identify, among a more or less heterogeneous group of compounds, those compounds having a particular feature, in the present case ligands binding to a specific target molecule. This purpose differs clearly from the expressed object of the experiments described in document D5 ("*to identify the DNA-binding surface of the ... Sso7d protein*"; see Abstract).

19. Consequently, as was the case for document D4, the disclosure of document D5 cannot be considered to anticipate the subject-matter of claim 1.

Document D12

20. Appellant II contended that the subject-matter of claim 1 lacked novelty also in view of document D12.

21. Document D12 describes the use of selective isotopic labelling with ^{15}N-containing amino acids and ^{15}N-^{1}H NMR spectra to study the interaction of the *Escherichia coli trp* repressor, a DNA-binding protein involved in the regulation of tryptophan biosynthesis, with tryptophan and an operator oligonucleotide. By measuring a series of heteronuclear correlation spectra of ^{15}N-labelled *trp* repressor and its complexes under the same experimental conditions, regions of the protein affected by ligand binding in solution are identified. All 50 amino acid residues studied in the *trp* repressor show measurable changes in amide ^{15}N and/or ^{1}H chemical shift upon the binding of tryptophan and/or the operator oligonucleotide, showing clearly that ligand binding has effects which are transmitted throughout almost the whole protein (see Abstract).

22. The purpose of the experiments described in document D12 is "*to characterize the trp repressor-tryptophan and trp repressor-tryptophan-oligonucleotide complexes*" (see page 601, right column, lines 11 to 13), and in particular to identify the regions of the *trp* repressor involved in ligand binding. Thus, for the same reasons given above in relation to D4, ie the lack of a clear and unambiguous disclosure of the purpose and technical

effect achieved by the process of claim 1 ("*to identify compounds that are ligands that bind to a specific target molecule*"), document D12 cannot be considered to anticipate the claimed subject-matter.

23. Summarizing the above, the board concludes that, with regard to any of documents D4, D5 and D12, the subject-matter of claim 1 must be considered to be novel within the meaning of Article 54 EPC.

Inventive step

24. For the assessment whether or not the claimed subject-matter involves an inventive step, the problem and solution approach applied by the Boards of Appeal requires that the closest prior art is first identified. In numerous decisions (cf. Case Law of the Boards of Appeal of the EPO, 4th edition, 2001, chapter I.D.3.1), the boards have established that the closest prior art should normally be a prior art document which discloses subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, so that a minimum of structural modifications is required. The aim is that the assessment process should start from a situation as close as possible in reality to that encountered by the inventor.

25. In the present case, several lines of argument were pursued by opponents-appellants based on different documents as the closest prior art, in particular documents D33, D26, D5, D68 and AVED1.

D33 as closest prior art in combination with D12 or D22

26. In the board's view, document D33 represents the closest prior art, because it discloses a process conceived for the same purpose as the process of claim 1, ie screening for compounds that are ligands to a specific target molecule (cf. paragraph 29 *infra*), and because among the documents cited as closest prior, D33 discloses the screening process that has the most relevant technical features in common with the claimed process, and requires less modification to arrive at the claimed subject-matter.

27. Document D33 addresses the question of ligand specificity for the kringle 5 domain of plasminogen, with the aim of investigating the mechanism for the interaction of plasmin(ogen) with fibrin in the context of blood clotting. The study focusses on the investigation of the aromatic spectrum of the kringle 5 domain in the absence (first spectrum; cf. Figures 2B, 4B and 8D) and presence of various ligands (second spectrum; cf. Figures 2 and 4, experiments A, C and D; and Figure 8, experiments A to C and E).

28. The binding specificity of various compounds which were either known or suspected ligands to the kringle 5 domain (arginine, benzamidine and a number of structurally related analogs; cf. Schemes 2 and 4) or to the kringle 1 and 4 domains (L-lysine and analogs; cf. Scheme 3) of plasminogen is investigated by one-dimensional ^{1}H NMR, with the goal to identify not only those compounds that bind to the kringle 5 domain, but also the aromatic side chains which are perturbed upon ligand binding (cf. lines 3 and 4 of the Abstract

"*The compounds tested as potential ligands include...*" and Figures 2, 4 and 8). Among the potential ligands tested, some compounds proved to be ligands and to bind to the kringle 5 domain (eg hexylamine; cf. page 3910, left column, first full paragraph), whereas others failed to bind to this domain (eg acetylarginine and acetyl arginine methyl ester; cf. page 3908, right column, lines 6 to 9).

29. It follows from the above that, contrary to appellant I's view, document D33 discloses, effectively, a series of individual tests that aim at the evaluation of different compounds in order to distinguish compounds which are ligands to the kringle 5 domain of plasminogen from those which are not. Hence, document D33 discloses a process of screening as understood by a person skilled in the art at the priority date of the patent in suit.

30. Starting from D33 as closest prior art, the technical problem to be solved can be defined as providing an improved process of screening for compounds that bind to a specific target molecule using NMR spectroscopy to monitor binding, which process is more reliable and less prone to "false positives" and "false negatives" than the screening processes known in the art.

31. It is undisputed that this problem is solved by a screening process according to claim 1, in which the **^{15}N-^{1}H NMR correlation spectra** obtained before and after exposing a **^{15}N-labelled target molecule** to one or a mixture of chemical compounds, are compared. Differences between the two spectra indicate the presence of one or more compound(s) which bind to the

target molecule. According to the patent, the claimed process avoids both "false positives" and "false negatives", especially when screening higher concentrations of potential ligands (cf. paragraphs [0031] and [0032] of the patent specification).

32. Thus, the sole question to be decided is whether, starting from D33 and having regard to the state of the art, in particular to the teachings of documents D12 and D22, it was obvious to the person skilled in the art at the priority date to try to modify the process of document D33 by (a) using a ^{15}N-labelled target molecule, and (b) comparing the two-dimensional ^{15}N-^{1}H NMR correlation spectra of the labelled target molecule generated before and after exposing the molecule to one or more potential ligand(s).

33. It was subject of dispute between the parties whether or not document D33 itself provides a motivation to modify the method described therein. Appellant II contended that the footnote 2 on page 3912 provided a motivation to use two-dimensional ^{15}N-^{1}H NMR spectroscopy for screening potential ligands to the kringle 5 domain.

34. The board disagrees with this view. In the cited footnote, it is stated that COSY (^{1}H-^{1}H NMR) spectra for kringle 5 were recorded only in the presence of excess ligand (either benzamidine or εACA), because a direct two-dimensional spectroscopic characterization of ligand-bound *versus* ligand-free kringle 5 was precluded by the line widths of the kringle 5 proton resonances as represented in Fig. 2B. Thus, in the experiment to which the cited footnote refers COSY (^{1}H-^{1}H NMR)

spectrometry is not used for screening potential ligands of kringle 5. Rather, the goal of this experiment is to better define those aromatic side chains which are perturbed upon binding of benzamidine and εACA to kringle 5 (cf. page 3912, section under the heading "Identification of the Kringle 5 Binding Site" starting at the bottom of the left column). It should be noted that the two compounds investigated (ie benzamidine and εACA) were known as ligands to plasminogen (cf. document D33, page 3906, right column, lines 1 to 6 of the first full paragraph, and page 3909, right column, lines 1 to 3 of the first full paragraph).

35. Hence, what the skilled person could, at most, infer from the cited footnote is that two-dimensional ^{1}H-^{1}H NMR spectroscopy suffers from certain drawbacks when used as a tool **for characterising the binding site of a ligand.** However, neither in footnote 2 nor elsewhere in D33 are any statements in relation to **screening** of potential ligands, that may motivate the skilled person to depart from the teaching of this document, ie the teaching of one-dimensional ^{1}H NMR spectroscopy as a screening tool.

36. Nonetheless, even if one assumes that it is the normal task of the skilled person to be constantly occupied with furthering the existing state of the art (cf. T 195/84, OJ EPO 1986, 121), the board is unable to find in the further prior art documents cited by appellant II any teaching that hints at a screening process as claimed, and specifically at two-dimensional ^{15}N-^{1}H NMR spectroscopy as a tool for screening potential ligands of a target molecule with the goal of avoiding "false positives" and "false negatives".

37. Document D22 reviews experimental NMR techniques for studies of protein-ligand interactions. The board notes that, whereas this document emphasises the usefulness of labelling the target molecule with various stable isotopes, *inter alia* ^{15}N and ^{13}C (cf. chapter "Isotope labelling" on page 762, left column; and paragraph bridging the left and right column on page 760), it fails to provide a specific teaching in respect of two-dimensional ^{15}N-^{1}H NMR spectroscopy and/or any advantages associated with this technique. In the section under the heading "Conclusion" (cf. paragraph bridging pages 764 and 765) to which appellant II pointed, NMR is praised as a versatile tool in combination with uniform isotope labelling, with the most exciting prospects for ligand binding studies being linked to site-specific isotope labelling techniques combined with the continuing refinement of the experimental NMR techniques. However, only multi-dimensional NMR techniques in general, and three-dimensional NMR spectra in connection with protein-ligand complexes, are mentioned.

38. Attention was drawn to the paragraph bridging the left and right column on page 760 of document D22. In this passage, reference is made to two-, three- and four-dimensional NMR experiments that support the ^{1}H resonance assignments of biomolecules, mainly in combination with selective or uniform enrichment with the stable isotopes ^{13}C **and** ^{15}N. Particular examples of **3D** solution structures are given. Thus, none of the cited passages of D22 supports the contention that this document gives the skilled person a hint towards two-dimensional ^{15}N-^{1}H NMR spectroscopy as a tool for

screening potential ligands that bind to a target molecule.

39. Additionally, document D12, in particular the passage in the first full paragraph of the left column on page 604, was cited. As stated above (cf. point 22 *supra*), D12 is concerned with the characterisation of the *trp* repressor-tryptophan and *trp* repressor-tryptophan-oligonucleotide complexes. In a preliminary experiment, uniformly ^{15}N labelled *trp* repressor was produced and its complex with tryptophan investigated by two-dimensional ^{15}N-^{1}H NMR spectroscopy. However, in spite of a better resolution compared to the one-dimensional ^{1}H NMR spectrum, only half of the crosspeaks were clearly resolved in the two-dimensional spectrum, and there was a number of overlapping crosspeaks in a narrow chemical shift range for both ^{1}H and ^{15}N (cf. page 603, left column, lines 5 to 10). Only when the repressor was selectively labelled with various [^{15}N] amino acids, most amide NH crosspeaks were resolved (cf., eg, page 604, left column, lines 17 to 20).

40. The board notes that, whereas the teaching of document D12 focusses on various strategies for selectively labelling the target molecule in order to increase the resolution in the NMR spectrum, the problem that a skilled person trying to improve the screening process described in document D33 sought to solve, was not necessarily a better resolution, but rather a reliable NMR tool which helped to reduce or even to avoid the number of "false positives" and "false negatives" resulting from the screening process. No hint in this direction is however found in document D12.

41. For the reasons given above, the board disagrees with the view of the opponents-appellants that the skilled person, in the expectation of some improvement in the reliability of the process described in D33, would have found in either document D12 or document D22 a hint that allowed him/her to arrive at the claimed process. In the absence of such a hint, it must be considered that, having regard to document D33 combined with the teachings of either D22 or D12, the claimed subject-matter involves an inventive step.

D26 as closest prior art in combination with any of D4, D12 and D15

42. Alternatively, appellant II considered document D26 as the closest prior art. In this document, a method based on mass spectrometry (electrospray ionization FTICR mass spectrometry, ESI-FTICR) is described for the characterisation of noncovalent complexes of proteins with mixtures of ligands. It should be noted that document D26 actually does **not** describe a process of screening, but only suggests that the method described therein may be relevant to the study of drug leads and potentially useful in screening libraries for tight-binding compounds (cf. page 8859, left column, lines 1 to 6).

43. Starting from D26, the technical problem to be solved may be defined as providing an improved process of screening for compounds that bind to a specific target molecule. The solution provided in the patent is a process of screening as defined in claim 1.

44. Appellant II held that document D26 itself provided a motivation to try to find a better tool for screening for ligands to a target molecule. However, whereas it might be true that the reported difficulties encountered when using ESI-FTICR for direct differentiation between complexes of the BCAII protein with inhibitors having very similar masses (cf. page 8860, right column, lines 1 to 3 of the first full paragraph) may encourage the skilled person to seek a different screening tool, the board cannot accept appellant II's argument that the skilled person would simply combine the teaching of document D26 with the teaching of any of documents D4, D12 and D15, all of which describe studies using two-dimensional ^{15}N-^{1}H NMR spectroscopy for investigating the modes of ligand binding to a target molecule.

45. Having in mind that the difficulties reported in document D26 were associated with similar masses of the ligands investigated, the skilled person would seek a spectroscopic method which is not dependent on the mass of the ligand. At the priority date various "mass-independent" spectroscopic methods were known in the art, among which the skilled person could choose. Moreover, even if one assumes that the skilled person could consider NMR spectroscopy as a suitable screening tool, different NMR techniques were available. See, for instance, document D22, where one-, two- and three-dimensional NMR techniques in combination with target molecules labelled with various isotopes are described.

46. Since appellant II has not provided any arguments as to why the skilled person, without any specific hint in the prior art, would have to choose among the available

spectroscopic methods **specifically** the two-dimensional ^{15}N-^{1}H NMR technique described in documents D4, D12 and D15, the board is not convinced that the claimed subject-matter lacks an inventive step in view of document D26 combined with any of these documents of the prior art.

Document D5

47. It was contended that, in view of the disclosure of document D5 alone, the claimed subject-matter lacked an inventive step. The arguments put forward in this respect were essentially the same as in connection with the issue of novelty (cf. Section XVI *supra*).

48. As stated above(cf. point 18 *supra*), the board is unable to find in document D5 a clear disclosure of a **screening** method. Moreover, no reasons have been given which justify the assertion that it would be obvious to the skilled person to try to use the two-dimensional NMR technique described in D5 as a screening tool. In the absence of such reasons, the objection of lack of inventive step based solely on document D5 must fail.

D68 as closest prior art in combination with D22

49. In document D68, ligand specificity of human plasminogen kringle 4 is investigated using one- and two-dimensional **^{1}H-^{1}H** NMR spectroscopy. In the reported study, a number of aliphatic and aromatic ligands are tested, with the aim of assessing (a) the extent to which hydrophobic interactions contribute to the kringle 4 binding affinity with aromatic ligands and (b) the role of the ligand's ionic groups in the

interaction with kringle 4 (cf. Abstract and page 11082, left column, first full paragraph). It is suggested that the knowledge derived from the study could assist in assessing potential ligands as antifibrinolytic drugs and in designing strategies to control plasmin(ogen) activity in vivo (cf. page 11082, left column, third full paragraph).

50. The strategy of the study described in document D68 is very similar to that of document D33, except for the latter being concerned with ligand binding to plasminogen at kringle 5 instead of kringle 4. Like document D33, D68 describes a series of tests which aim at the evaluation of a number of compounds in order to distinguish compounds that are ligands to a particular domain of plasminogen from those which are not, the tests being carried out for each compound individually. Thus, document D68 is also considered to disclose a process of screening using NMR spectroscopy as screening tool.

51. Consequently, starting from D68 as closest prior art the problem to be solved can be defined in the same manner as above in connection with document D33 (cf. point 30 *supra*).

52. As stated above in another context (cf. points 37 and 38 *supra*), the board is unable to find in document D22 - now cited in combination with document D68 - any teaching that hints at a screening process as claimed, and specifically at two-dimensional ^{15}**N-**^{1}**H** NMR spectroscopy as a tool for screening potential ligands of a target molecule. In view of the similar disclosure content of documents D33 and D68, and since reference

was made essentially to the same passages of document D22 discussed in connection with appellant II's objection based on document D33 as closest prior art, the reasons given above also apply, *mutatis mutandis*, to the combination of documents D68 and D22.

AVED1 as closest prior art in combination with D22

53. Document AVED1 relates to a study of novel inhibitors bound to farnesyl-protein transferase using NMR spectroscopy, in particular two-dimensional transferred nuclear Overhauser enhancement spectroscopy (TRNOESY). This technique is said to be ideally suited for studying weakly bound ligands in fast exchange with a macromolecule such as a protein (cf. Abstract and page 682, paragraph bridging the left and right columns). It is stated in AVED1 that the information derived from the reported study may become an aid in the design of future inhibitors which are selective, potent and exhibit appropriate pharmacological properties (cf. paragraph bridging pages 684 and 685). It is noteworthy that the investigation described in AVED1 focusses on the NMR spectrum of the **ligand** in the presence and absence of the target molecule.

54. Starting from document AVED1 as closest prior art, the problem to be solved can be defined in the same manner as above (cf. point 30 *supra*).

55. As a motivation to improve the screening process described in document AVED1, the opponents-appellants pointed to the sentence bridging pages 682 and 683, stating that, under certain circumstances, moderate non-specific binding was observed that severely

complicated the interpretation of the TRNOEs. However, they pointed also to the instructions given in the document to deal with this difficulty (cf. page 683, starting on line 16 of the left column "*In order to minimize non-specific binding, ...*"). Thus, being provided with the solution to the problem mentioned in the document, the skilled person would not have any motivation to depart from the screening tool described in document AVED1, which was, reportedly, ideally suited for weak binding ligands and, consequently, possibly avoided the problem of "false negatives".

56. But even if one acknowledges that the person skilled in the art could try - on his/her own initiative - to improve the screening process described in AVED1, the board does not see that the skilled person could find in document D22 a hint at the claimed screening process, in particular at two-dimensional ^{15}N-^{1}H NMR spectroscopy as a tool for screening potential ligands of a target molecule. The reasons given above in connection with document D33 as closest prior art (cf. paragraphs 37 and 38 *supra*) are equally valid in this context.

57. Summarising the above: having considered each and every line of argument put forward by the opponents-appellants, the board is not convinced that the screening process of claim 1 as granted lacks an inventive step. No arguments against an inventive step in relation to dependent claims 2 to 4 as granted have been submitted on appeal.

Amendments to the description

58. The board is satisfied that the amendments to the description do not introduce any subject-matter which extends beyond the content of the application as filed (cf. Article 123(2) EPC), or extend the protection conferred by the patent as granted (cf. Article 123(3) EPC).

Order

For these reasons it is decided that:

1. The appeal filed by Sanofi-Aventis Deutschland GmbH is inadmissible.

2. The decision under appeal is set aside.

3. The case is remitted to the first instance with the order to maintain the patent on the basis of claims 1 to 4 as granted, the amended description filed during the oral proceedings and the drawings as granted.

The Registrar: The Chairman:

A. Wolinski L. Galligani