DECISION
of 26 July 2004

Case Number: T 0729/00 - 3.3.4
Application Number: 89902686.8
Publication Number: 0403506
IPC: C12Q 1/02

Language of the proceedings: EN

Title of invention: Method of screening for protein inhibitors and activators

Patentee: HOUSEY PHARMACEUTICALS, INC.

Opponents: Hoechst AG
Roche Diagnostics GmbH
Boehringer Ingelheim GmbH

Intervener: Bayer AG

Headword: Screening method/HOUSEY

Relevant legal provisions: EPC Art. 54, 56, 83, 87, 123(2)

Keyword: "Inadmissible amendment - (no)"
"Sufficiency of disclosure - (yes)"
"Priority - (yes)"
"Novelty - (yes)"
"Inventive step - (no)"
Decisions cited:
-

Catchword:
-
Case Number: T 0729/00 - 3.3.4

DECISION of the Technical Board of Appeal 3.3.4 of 26 July 2004

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Decision under appeal: Interlocutory decision of the Opposition  
Division of the European Patent Office posted  
26 April 2000 concerning maintenance of  
European patent No. 0403506 in amended form.

Composition of the Board:  
Chairwoman: U. M. Kinkeldey  
Members: G. L. Alt  
S. C. Perryman
Summary of Facts and Submissions

I. These appeal proceedings relate to the decision of the Opposition Division maintaining in amended form European patent No. 0 403 506 entitled "Method of screening for protein inhibitors and activators" and claiming a priority date of 10 February 1988.

II. Claim 1 as filed read:

"1. A method of determining whether a substance is an inhibitor or activator of a protein whose production by a cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in said cell per se, which comprises:
(a) providing a first cell line which produces said protein and exhibits said phenotypic response to the protein;
(b) providing a second cell line which produces the protein at a lower level than the first cell line, or does not produces the protein at all, and which exhibits said phenotypic response to the protein to a lesser degree or not at all;
(c) incubating the substance with the first and second cell lines; and
(d) comparing the phenotypic response of the first cell line to the substance with the phenotypic response of the second cell line to the substance."

Independent Claims 1 and 3 as granted read:

"1. A method of determining whether a substance is an inhibitor or activator of a protein whose presence in a cell evokes a responsive change in a phenotypic
characteristic other than the level of said protein in said cell per se, which comprises:
(a) providing a cell which overproduces said protein and exhibits said phenotypic response to the protein;
(b) incubating said cell with said substance; and
(c) determining whether said cell exhibits a responsive change in a phenotypic characteristic."

"3. A method of determining whether a substance is an inhibitor or activator of a protein whose presence in a cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in said cell per se, which comprises:
(a) providing a first cell which overproduces said protein and exhibits said phenotypic response to the protein;
(b) providing a second cell which produces the protein at a lower level than the first cell, or does not produce the protein at all, and which exhibits said phenotypic response to the protein to a lesser degree or not at all;
(c) incubating the first and second cell with the substance; and
(d) comparing the phenotypic response of the first cell to the substance with the phenotypic response of the second cell to the substance."
cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in said cell per se, which comprises:
(a) providing a cell line which overproduces said protein and exhibits said phenotypic response to the protein;
(b) incubating said cell line with said substance; and
(c) comparing the phenotypic response of said cell line of (a) to the substance with the phenotypic response of a control cell line to the substance to determine whether said cell line of (a) exhibits a responsive change in a said phenotypic characteristic."

Claim 3 as found acceptable by the Opposition Division was the same as claim 1 of the sole request before the Board (see section IV below), except that in line 3 of feature (b) it grammatically correctly read "produce" rather than "produces".

IV. Claim 1 of the sole request maintained during oral proceedings before the Board read (for easier comparison changes compared to the corresponding claim 3 as granted are shown in bold italics):

"1. A method of determining whether a substance is an inhibitor or activator of a protein whose presence in a cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in said cell per se, which comprises:
(a) providing a first cell line which overproduces said protein and exhibits said phenotypic response to the protein;
(b) providing a second cell line which produces the protein at a lower level than the first cell line, or
does not produce [sic] the protein at all, and which
exhibits said phenotypic response to the protein to a
lesser degree or not at all;
(c) incubating the first and second cell line with the
substance; and
(d) comparing the phenotypic response of the first cell
line to the substance with the phenotypic response of
the second cell line to the substance.

V. The patent had been opposed by three opponents on the
grounds of Article 100(a) in combination with
Article 54 and 56 EPC, Article 100(b) EPC and
Article 100(c) EPC.

The opposition division decided to maintain the patent
on the basis of claims amended compared to the claims
as granted considering that the requirements of
Articles 123(2) EPC were met, and that in the absence
of any experimental evidence that the invention could
not be got to work, the opponents had not discharged
their burden of proof in relation to the sufficiency
requirements of Article 83 EPC. Novelty was
acknowledged over the documents cited as novelty
destroying before the opposition division (of which
only documents A7, A9 and A12 were also relied on as
novelty destroying in the appeal proceedings) as none
showed all the technical features required by the
claims. Novelty over document A7 was acknowledged
because it was considered that it did not show a direct
interaction between the inhibitor and the enzyme
forming the protein of interest. Novelty over document
D9 was acknowledged because the substance tested
removed the protein from the system rather than having
a direct effect on its expression. Novelty over
document A12 was acknowledged because it was not clear what precise mechanism caused the changes in phenotypic response there reported, or that a protein of interest was responsible. For the purpose of inventive step either document A7 or A12 was considered to represent the closest prior art, and the problem was formulated as the provision of (i) a rapid and easy method for the detection of specific chemical activators and inhibitors of a protein which interact directly with the protein and modulate its cellular activity(ies) in a useful manner. None of the documents before the opposition division taken singly or together suggested the claimed system.

VI. Notices of appeal were filed by all three opponents. Opponents 2 and 3 subsequently withdrew their appeals.

VII. A notice of intervention was filed by the intervener having been sued for infringement under the German patent resulting from the patent in suit, and at the same time the opposition fee and the appeal fee were paid.

VIII. The board sent a communication setting out its preliminary opinion on the issues.

IX. Oral proceedings were held on 22, 23 and 26 of July 2004 at the end of which the Board announced its decision.

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


XI. Insofar as they relate to the subject matter of Claim 1 before the Board, the arguments by the appellant and the intervener can be summarized as follows:


Amendments (Article 123(2) EPC)

- Claim 1 as granted referred in its preamble to determining whether a substance is an inhibitor or an activator of a protein whose presence in a cell evoked a responsive change, whereas Claim 1 as filed in its preamble referred to a protein whose production by a cell evoked a responsive change. Since a protein might be present in a cell without being actively produced in it, claim 1 as granted encompassed conditions not covered by the original application documents.

Sufficiency of disclosure (Article 83 EPC)

- The patent referred only to distinguishing between substances which specifically inhibit the protein of interest and substances which affect cell morphology or growth by other mechanisms. If, as argued by the patentee, the invention was supposed to enable the user to distinguish between direct and indirect inhibitors, the information in the patent was insufficient for this to be achieved and certainly the technical features listed in the claim were insufficient for this result to be achieved.

- For example, it would not be possible to distinguish between a substance which bound to the gene coding for the protein of interest causing a reduction in its expression in the cell line, and a substance binding to the protein of interest and inhibiting its enzymatic activity. The observed phenotypic effect could well be the same, and other tests would be needed to distinguish the two cases.
The term "overproducing" only made technical sense when comparing the amount of protein of interest produced by two different cell lines.

If "overproducing" by itself meant production of a quantity of the protein of interest at a level making it particularly suitable for determining "direct" inhibitors or activators, the skilled person was not told that such a level existed or how to find it, nor was it plausible that such a level could be achieved for all possible proteins of interest for all cell lines. If "overproducing" had to be given such a special meaning the patent description was insufficient.

Further, in view of the lack of information as to what phenotypic characteristics due to a POI should be looked for in what cell line, the invention was not disclosed in a manner sufficiently clear and complete for it to be carried out without undue burden by a person skilled in the art over the whole scope of the claims.

Novelty (Article 54 EPC)

Claim 1 as granted referred in its preamble to determining whether a substance is an inhibitor or an activator of a protein whose presence in a cell evoked a responsive change, whereas Claim 1 of the priority document in its preamble referred to a protein whose production by a cell evoked a responsive change. Since a protein might be present in a cell without being actively produced in it,
claim 1 as granted encompassed conditions not covered by the priority document, and so was not entitled to priority. Thus documents A26 and A27 were prior art and destroyed novelty.

- Each of documents A7, A9, A12, A51, A52, A58, A72, A73 and A94 took away the novelty of the subject-matter of at least claim 1 because they disclosed steps (a) to (d) of the claimed method.

- Document A58 and document A72 even performed the steps with the objective of determining substances inhibiting the activity of a specific protein.

**Inventive step (Article 56 EPC)**

- Insofar as claim 1 was novel at all over document A58, the difference was trivial, as document A58 already compared the effect of an inhibitor on a test cell line with the protein of interest causing a phenotypic response, with that of an inhibitor on a control cell line not showing this phenotypic response to the presence of the protein. Claim 1 could only be regarded as directed to an alternative solution, and document A58 either by itself or in combination with common general knowledge made this alternative obvious.

- Further a combination of documents A72 and A12 rendered the subject-matter of the claims obvious. Document A72 taught a screening system using a test cell line producing the protein of interest, and control cell line producing only about 1% of the protein of interest of the test cell line. Even if
novelty existed because here a control cell line was used which was "underproducing" relative to the test cell line, the skilled person would see that the essence of the method was the comparison of two cell lines producing the protein of interest at different levels, so it would be an obvious alternative to make such pairs of cell lines by making a higher producing test cell line from a lower (or nil) producing control line by inserting a gene coding for the protein of interest by standard methods of genetic manipulation as would be common general knowledge or could be derived from document A12, which disclosed such a pair of cells in the context of screening for substances enhancing tumour growth.

XII. Insofar as they relate to the subject matter of Claim 1 before the Board, the arguments by the respondent can be summarized as follows:

Amendments (Article 123(2) EPC)

- Both present Claim 1 and Claim 1 as originally filed referred in feature (a) to providing a cell line which overproduces said protein and exhibits said phenotypic response to the protein. That present Claim 1 referred in its preamble to a protein whose presence in a cell evokes a responsive change in a phenotypic characteristic, rather than to a protein whose production in a cell evokes this change, as in the preamble of Claim 1 as originally filed, merely emphasized, consistent with the originally filed description, that the response is due to the presence of the protein. The change in wording did not contravene Article 123(2) EPC.
Sufficiency of disclosure (Article 83 EPC)

- None of the steps of the claimed method exceeded the normal experimental capabilities of a person skilled in that field. Therefore there was neither an undue burden involved in carrying out the method nor was there a failure to disclose the claimed method sufficiently over the whole breadth of the claim. There was certainly no evidence that anyone had tried to carry out the method but failed.

- For sufficiency, the skilled person only had to be able to find one cell line in which the presence of the protein of interest caused a suitable phenotypic response.

- The reference to "determining whether a substance is an inhibitor or activator" meant determining whether it was a direct inhibitor or activator, in accordance with the ordinary dictionary meaning of "determine".

- However, determining whether a substance was an inhibitor or activator meant screening out likely candidates from a larger pool. It meant a high degree of likelihood, not absolute 100% certainty: there would always be some degree of uncertainty for such a screening test.

Novelty (Article 54 EPC)

- That Claim 1 referred in its preamble to protein whose presence in a cell evoked a responsive change,
whereas Claim 1 of the priority document in its preamble referred to a protein whose production by a cell evoked a responsive change did not deprive present Claim 1 of priority, as the priority document made clear the phenotypic change was due to the presence of the protein, and Claim 1 still required that the cell line produce the protein. Thus documents A26 and A27 were not prior art.

- None of the documents cited against novelty related to a method of determining whether a substance is an inhibitor or an activator of a protein. The absence of this limiting feature required by the preamble of the claim was in itself enough to establish novelty.

- Document A58 compared the effects of a substance on a cell which produced a thermally sensitive mutant at two different temperatures, only at one of which the phenotypic response occurred. This was not what was required by the claim, and was not a generally applicable method. The only comparison made between a cell producing a protein and one not producing it was in relation to further characterising a substance which had already been determined to be an inhibitor.

- Further document A58 was concerned rather in inhibiting the effect of an oncogene than in finding substances that inhibited a protein.

- Document A72 disclosed a method using a mutant producing the protein of interest at a low level, rather than creating an overproducing cell line.
Further for the comparison made in document A72, it was essential for growth of the mutant line that the protein product, thymidine (dThd), be added, so that the comparisons of the two cell lines related to the presence of both the inhibitor and the protein product dThd, which was not as claimed.

Inventive step (Article 56 EPC)

- The contribution of the patent to the art was the idea that the phenotypic characteristic could be observed in specifically engineered cells which overproduced the protein of interest and that this response could be utilized for the identification of modulators of said protein, and the idea that this was a method capable of general application to identify the inhibitors and activators of any protein. No hint of this appears in any of the cited documents.

- It was a further merit of the invention, as recognized by the opposition division, that it allowed the person skilled in the art to determine direct inhibitors or activators.

- As document A72 was concerned with finding modulators of a protein it should be treated as the closest prior art, in relation to which the problem to be solved could be formulated as providing an improvement. This problem was solved by the patent in suit by the provision of an overproducing cell line.
XIII. Requests

The appellant (opponent 1) and the intervener (opponent 5) requested that the decision under appeal be set aside and that the European patent No. 0 403 506 be revoked.

The respondent (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of request I filed at oral proceedings.

Reasons for the Decision

Parties and admissibility

1. The Appellants (Opponents 1) filed an appeal meeting the requirements of Articles 106 to 108 and Rule 64 EPC. This has not been disputed by the Respondents (Patentee). The appeal is admissible.

2. The Intervener filed an intervention with a reasoned statement within three months of being sued for infringement under the patent in suit as it extends to Germany, and paid the opposition fee and the appeal fee. This has not been disputed. The intervention meets the requirements of Article 105 EPC and is admissible as certainly all fees due have been paid. As the intervener is not asking for reimbursement of the appeal fee, the question of what fees precisely are due from an intervener who intervenes in a pending appeal does not have to be decided for the purpose of these proceedings.
3. Opponents 2 filed an appeal but subsequently withdrew their opposition and the appeal. Opponents 3 filed an appeal but subsequently withdrew their opposition. In accordance with the view taken in the established case law of the Boards of Appeal, withdrawal of the opposition is also taken as withdrawal of the appeal. By virtue of Article 107 EPC second sentence Opponents 2 and 3 are parties to the appeal by Opponents 1. However, in accordance with the view taken in the established case law of the Boards of Appeal by withdrawal of their oppositions they are not parties on any substantive issues, but only for the purpose of ancillary issues such as those relating to costs. No such issues have been raised, so that Opponents 2 and 3 are purely nominal parties.

4. As a result of the intervention and of the appeal additional documents relevant for novelty and inventive step have been introduced into the proceedings, but the grounds of invalidity to be considered remain the same as before the Opposition Division. In view of the fact that none of the parties submitted that the new documents necessitate a remittal of the case to the first instance, that infringement proceedings are pending, and that the Board considers it appropriate that the issues of sufficiency and inventive step should be considered together, the Board has decided to exercise its discretion under Article 111 EPC in favour of deciding all relevant issues without remittal.
Amendments (Article 123(2) EPC)

5. Claim 1 of the application as originally filed referred to:

"A method of determining whether a substance is an inhibitor or activator of a protein whose production by a cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in said cell per se, which comprises: (a) providing a first cell line which produced said protein and exhibits said phenotypic response to the protein;..."

Claim 1 of the present main request contains the same wording except that instead of "whose production by" it states "whose presence in". The skilled reader would normally assume that "production of protein...evokes a change in a phenotypic characteristic" refers to the presence of the produced protein evoking this change, and this is confirmed by the passages on page 9, lines 3 to 6 of the application as originally filed reading "The present method is intended for use in identifying potential chemical inhibitors or activators of enzymes, receptors, or any proteins which have effects upon cell prototype". Thus the change in wording merely emphasizes that the phenotypic response is due to the presence of the protein. The requirement in feature (a) of claim 1 as originally filed that the cell line produce said protein remains, and the amendment introduces no new subject matter. The Board thus sees no amendment here that contravenes the requirements of Article 123(2) EPC.
Sufficiency of disclosure (Article 83 EPC)

6. Two separate lines of attack on the patent were formulated under Article 83 EPC.

   (a) In view of the argument by the respondent that the invention enabled the distinction between a direct inhibitor and an indirect one of a protein of interest ("POI"), it was argued that as use of the technical features required by claim 1 would not enable such a distinction, and the description did not give any clear indication how to make up for this, there must be insufficiency.

   (b) Secondly it was argued that in view of the lack of information as to what phenotypic characteristics due to a POI should be looked for in what cell line, the invention was not disclosed in a manner sufficiently clear and complete for it to be carried out without undue burden by a person skilled in the art over the whole scope of the claims.

7. The patent refers only to distinguishing between substances which specifically inhibit the protein of interest and substances which affect cell morphology or growth by other mechanisms in that they will have a greater effect on the test lines than on the control lines (see for example page 3, lines 17 to 19), but not to distinguishing whether specific inhibitors act directly or indirectly. Even though it was argued by the patentee in connection with the inventive contribution made, that the invention was supposed to enable the user to distinguish between direct and
indirect inhibitors, the board does not see that such enablement can be treated as a technical feature of claim 1, or as something necessarily achievable by solely carrying out the method of claim 1. For a preferred embodiment of the invention, it is suggested that production of the protein of interest by the first cell line be maximised relative to that of the second cell line to achieve a sensitive test (see patent page 5, lines 22 to 23), but this is not a requirement of claim 1 nor is it plausible that this could be done to an extent that would allow one to distinguish between direct and indirect inhibitors for all possible cases.

8. The board agrees with the appellant and the intervener that claim 1 does not state technical features which would enable a skilled person to distinguish between a direct and an indirect inhibitor, whatever precise meaning is to be attributed to these terms, and that the specification does give other information which would allow the skilled person to operate the method of claim 1 to make this distinction. Rather, as admitted by the respondent during the oral proceedings, it would take some further tests to make such a distinction. But the Board also concludes that being able to make such a distinction is not part of the subject matter of claim 1, so being unable to make the distinction cannot lead to a finding of insufficiency, rather it may be relevant when it comes to considering novelty and inventive step over the prior art.

9. Regarding the argument relating to undue burden over the scope of the claim, the Board takes as starting point for someone wishing to practice the invention,
that he or she knows of a cell which shows a suitable type of phenotypic response to the POI, and which response it would be desirable to suppress or increase respectively. Only this starting point gives the skilled person any reason for wishing to find out about inhibitors or activators. It seems plausible that from this starting point an overproducing line can be achieved, at least by the exemplified by the genetic engineering method of inserting a gene coding for the POI. Certainly no evidence has been provided that this would be impossible. Thus sufficiency can be acknowledged.

10. It should be noted that on the view thus taken by the Board, neither selecting a POI causing a particular phenotypic response in the cell, nor distinguishing between direct and indirect inhibitors can be treated as any part of the inventive contribution for the purpose of assessing inventive step.

Novelty (Article 54 EPC)

11. Lack of novelty was alleged in relation to documents A7, A9, A12, A52, A58, A72, A73 and A94, all published before the claimed priority date of the patent in suit, and during the written proceedings also in relation to documents A26 and A27, whose authors included the inventor of the patent in suit, published between the claimed priority date and the filing date, on the basis that the claims as granted were not entitled to the priority claimed.
12. The wording of Claim 1 of the priority document is identical to that of Claim 1 of the application as originally filed, and the first part reads:

"A method of determining whether a substance is an inhibitor or activator of a protein whose production by a cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in said cell per se, which comprises: (a) providing a first cell line which produced said protein and exhibits said phenotypic response to the protein;..."

Claim 1 of the present main request contains the same wording except that instead of "whose production by" it states "whose presence in". As already stated in point 3 above in relation to an objection under Article 123(2) EPC, the skilled reader would normally assume that "production of protein...evokes a change in a phenotypic characteristic" refers to the presence of the produced protein evoking this change, and this is confirmed by the passage on page 3, lines 17 to 21 of the priority document reading: "In brief, the method which we describe herein involves the generation of a cell line purposefully engineered to detect both stimulatory and inhibitory agents which are absolutely specific for any given protein which affects the cultural or morphological characteristics of the cell."

This makes clear that it is the [presence of the] protein which affects the phenotypic characteristic. Present Claim 1 is thus entitled to the priority claimed, and documents A26 and A27 are not part of the state of the art for the purposes of Articles 54 or 56.
EPC, so that it is not necessary to consider their content.

Document A58

13. Document A58 entitled in its English translation "A New Approach to the Development of Antitumour Agents using Cells Expressing Oncogenes" is concerned with screening substances that inhibit the action of oncogenes. It says "..We therefore argued that, if we could find a substance that acted selectively, discriminating between normal cells and cancer cells expressing some specific oncogene, a therapeutic effect against the cancer might be expected, and asked ourselves what cells would be best suited to this purpose. Our first choice of oncogene was src, the gene whose mechanism of action has been studied in most detail. When oncostatic substances are to be screened using cancer cells cultured in vitro, it is desirable to pair the cancer cells with normal cells providing a control. Cells incorporating a ts [temperature sensitive] oncogene were therefore seized on (Figure 1). Thus with cells of this kind, the cancerous and normal states can be created simply by changing the temperature of culture, and as the difference is simply a matter of whether or not the target oncogene is functional, this pairing was considered ideal for comparing cancerous and normal states. Moreover, the difference was clearly reflected in the cell morphology (Figure 2) It was hence supposed that any substance that converted the cell at the 33°C permissive temperature into the same form as at 39°C and maintained this form must be suppressing the oncogene...."
14. The authors describe transforming a rat kidney cell line (NRK) using Rous Sarcoma Virus (RSV) that has a temperature-sensitive (ts) mutation in its src oncogene, and using this to find oncogenes. In connection with one inhibitor they found using this method, oxanosine, the authors describe (pages 7 and 8) experiments to elucidate the mechanism of action of oxanosine, as this was more active against cells expressing the src oncogene. They state "...To eliminate mechanisms such as "more potent action on rapidly growing cells", the concentration of serum in the culture medium was adjusted to give roughly the same rate of growth at both temperatures. This meant conducting the culture at two temperatures at the same serum end-concentration of 10% (growth of the normal cells is highly serum-dependent). By way of control experiment, it was confirmed beforehand that there was no difference at either 33°C or 39°C in the growth inhibitory activity of oxanosine towards RSV-uninfected NRK cells...".

The authors also confirmed that the effects observed were attributable to the expression product of the src gene, the protein p60src, a tyrosine kinase, which at 33°C is functional and causes the cancerous phenotype to be exhibited by the cells, but when the temperature is raised to 39°C the p60src tyrosine kinase activity is lost and the normal phenotype is exhibited.

15. That the authors of document A58 are primarily interested in suppressing the effects of the src gene, does not alter the fact that they are also describing a method of finding an inhibitor of the src gene protein expression product p60src, a tyrosine kinase. Finding inhibitors of proteins cannot be treated as an end in
itself, but rather must be considered in a context where such inhibition serves some desired purpose, and document A58 explicitly relates to a situation where it is desirable to find inhibitors of the protein p60src.

16. Before assessing the disclosure of document A58 in terms of the features of claim 1, the meaning to be attributed to "overproducing" in the context of the patent text as a whole needs to be considered. At page 2, lines 4 to 5 it is stated "...By "overproduced" I mean that the POI is expressed at higher levels in the genetically manipulated cell line than in the original cell line..." and at page 5, lines 22 to 24 it is stated "Generally speaking, it is preferable to maximize the ratio of production by the "overproducing" cell line to production by the "native" line. This is facilitated by selecting a host cell line which produces little or no POI, and introducing multiple gene copies and/or using high signal strength promoters...". In the context of claim 1, a first cell line can thus be described as "overproducing" relative to a second cell line if it produces more of the POI than the second cell line, and a cell line producing the POI will be "overproducing" relative to any native cell line which does not produce the POI at all.

17. Considering the disclosure of document A58 in terms of the features of claim 1, it discloses a method of determining whether a substance is an inhibitor or activator of a protein (p60src tyrosine kinase) whose presence in a cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in said cell per se, which comprises: (a) providing a first cell line (the RSV-transformed NRK
cell line) which overproduces said protein and exhibits said phenotypic response to the protein. Document A58 also refers to using the untransformed native NRK cell line which necessarily does not produce the protein (p60\textsuperscript{src} tyrosine kinase) and so does not exhibit said phenotypic response at all. This meets the requirement of the feature (b) of the claim.

18. While document A58 discloses incubating the first cell line (RSV(ts)-transformed NRK cell line) with potential inhibitors it describes determining the inhibitory activities by comparing the effect of potential inhibitors being screened on the same cell at two different temperatures, and not by comparing the response of a transformed cell with that of the untransformed native NRK cell line, so that features (c) and (d) of claim 1 are not literally met. Only for the case of elucidating the mechanism of an already selected inhibitor, oxanosine, is the phenotypic response of a transformed cell to the inhibitor compared to the phenotypic response of the untransformed cell, which as the respondent argued could be treated as obtaining further information on the properties of an already identified inhibitor, rather than determining whether or not the substance is an inhibitor.

19. On the narrow view of novelty taken in the established case law, it cannot be said that document A58 provides a clear and unambiguous disclosure of all the features of claim 1 in combination.
Document A7

20. Document A7 is an earlier publication by the same authors as document A58 also relating to their work on identifying inhibitors of p60\(^{src}\), the src gene product. However it gives less detail, and as for document A58 no comparison of the transformed cell with the native cell is described for the purpose of identifying inhibitors, so that this document does not anticipate claim 1.

Document A72

21. Document A72 discloses a pair of cell lines useful for detecting thymidilate synthetase inhibitors. In terms of the features of claim 1, this is a method of determining whether a substance is an inhibitor of a protein (thymidilate synthetase) whose presence in a cell evokes a responsive change in a phenotypic characteristic other than the level of said protein in said cell per se (namely the rate of growth of the cells), which comprises (a) providing a first cell line (the wild-type carcinoma cell line FM3A/O) which exhibits said phenotypic response to the protein, and overproduces it relative to a second cell line (FM3A/TS\(^-\)) which produces only about 1% of the quantity of protein.

22. The second cell line (FM3A/TS\(^-\)) is stated as not growing in the absence of thymidine (dThd), so this has to be added to allow the second cells to grow at all (the phenotypic characteristic being compared). The comparisons made are between the effects of the inhibitor on the first cell line with respectively the addition of 0\(\mu\)M dThd, 5\(\mu\)M dThd, 20\(\mu\)M dThd, compared to
addition of the inhibitor to the second cell line with the addition of 5µM dThd, 20µM dThd. It is thus not clear that the requirements of claim 1 are precisely met, as it is not just the effect of the inhibitor which is being looked at, but the effect of the inhibitor at a certain level of dThd. Taking a strict view on this the Board considers that lack of novelty over document A58 has not been established.

Document A9

23. Document A9 reports on whether the phenotype transformation produced by neu oncogene product p185, can be reversed by antibodies to this product. In one of the experiments (Figure 5) two culture dishes were seeded with cells of a cell line transformed with the gene encoding the neu oncogene and one dish was seeded with the parental, non-transformed cell line. To one of the dishes harbouring the transformed cell line antibody was added, not however to the other one with the untransformed cells. Upon addition of the antibody the neu-transformed cell line looses its ability to form foci in soft agar and the colonies have a morphology similar to those of the parental line. Thus, the substance - monoclonal antibodies - is only added to the test cell line and not the control cell. Consequently, the method disclosed in document A9 lacks at least the feature of claim 1 that the inhibitor to be tested is added also to the second cell line.

Document A94

24. The authors of document A94 investigate whether mouse cells transformed with the coding region of
beta2-adrenergic receptors express functional receptor proteins. The receptors stimulate the production of c-AMP via a system of different enzymes. Amongst others the following experiment was performed: the cell line expressing the receptor protein and the native cell line without receptor expression were contacted with a known stimulator of the receptor. It was found that only the receptor expressing cells were stimulated by the substance. This does not anticipate the method of claim 1 because there is no phenotypic response of the cell to the protein before addition of the substance. Only after the substance is added can the response - change in cAMP concentration - be measured. Moreover, in document A94 it is explicitly stated on page 14844, left column, first paragraph that the growth characteristics of the transfected cells are identical to the parent cell line, consistent with the view that receptor expression alone does not evoke any effect.

Document A12

25. Document A12 entitled "Oncogene-Induced Transformation of a Rat Embryo Fibroblast Cell Line is Enhanced by Tumor Promoters", does not mention the words inhibitor or activator, and it is not clear that any of the observations reported in it are necessarily referable to an inhibitor or activator of a protein whose presence in a cell involves a phenotypic change, or whether they have to be attributed to much more complicated interactions. This is in itself sufficient for considering document A12 as incapable of anticipating claim 1.
Document A51

26. Document A51 entitled "Studies on a new epidermal growth factor-receptor kinase inhibitor, Erbstatin, produced by MH435-hF3" relates to the screening of culture filtrates of actinomycetes for inhibitors of tyrosin protein kinase. The document refers to the inhibition of the growth of rat kidney cells transformed by a similar temperature sensitive mutant (src\textsuperscript{ts} -NRK) of Rous sarcoma virus as that mentioned in document A58, but it is not stated that the effect of the inhibitor on the untransformed and the transformed cell lines was compared, so that there is no clear and unambiguous anticipation of feature (d) of claim 1.

Document A52

27. Document A52 entitled "A Factor Present in Fetal Calf Serum Enhances Oncogene-Induced Transformation of Rodent Fibroblasts" concludes with a final paragraph reading "...The results obtained in the present study may have considerable biologic importance, since they indicate that FCS normally contains a factor that markedly enhances the transformation of cells carrying an activated oncogene. This finding may provide insights into endogenous factors that enhance the multistage carcinogenic process following the mutational activation of specific oncogenes." The subject reported on is very complex and as in the case of document A12 it is not clear that any of the observations reported in document A52 are necessarily referable to an inhibitor or activator of a protein whose presence in a cell involves a phenotypic change, or whether they have to be attributed to much more
complicated interactions. This is in itself sufficient for considering document A52 as incapable of anticipating claim 1.

Document A73

28. Document A73 entitled "Differential Responsiveness of myc and ras-Transfected Cells to Growth Factors: Selective Stimulation of myc-Transfected Cells by Epidermal Growth Factor" reports on the investigation of complex factors governing tumour growth. As in the case of document A52, it is not clear that any of the observations reported in it are necessarily referable to an inhibitor or activator of a protein whose presence in a cell involves a phenotypic change, or whether they have to be attributed to much more complicated interactions. This is in itself sufficient for considering document A73 also as incapable of anticipating claim 1.

Inventive step (Article 56 EPC)

Closest prior art and problem to be solved

29. Document A58 discussed above in points 13 to 19, relates to a method of finding inhibitors to the protein gene product of an oncogene, one of the main areas suggested in the patent for application of the claimed method. As discussed above, document A58 has all technical features required by the claim except that it chiefly determines the inhibitory activities by comparing the effect of potential inhibitors being screened on the same cell at two different temperatures, and not by comparing the response of a transformed cell
with that of the native cell. But for the case of
elucidating the mechanism of an already selected
inhibitor, oxanosine, the phenotypic response of a
transformed cell to the inhibitor is compared to the
phenotypic response of the untransformed cell. Both its
field and the similarity to the method now claimed make
it the appropriate starting point for considering
inventive step.

30. Document A58 is specifically concerned with determining
inhibitors of protein p60$^{src}$, the product of the
oncogene src. For this protein for which a temperature
sensitive variant was known, the prior art seems, if
anything, more convenient than the exact method of
claim 1, so that the problem to be solved cannot be
viewed as achieving an improvement. Rather for someone
interested in an oncogene and inhibitors of its protein
product, which was known to cause a particular
morphological response, the problem would arise, fairly
and without hindsight, whether he would derive from
document A58 in an obvious manner any way of testing
for inhibitors of the oncogene protein product of
interest to him. For reasons already discussed above in
connection with sufficiency and summarized in point 10
above, no more ambitious problem can be regarded as
solved.

31. The skilled person would see that because his gene
product of interest caused an observable morphological
change the method of document A58 could be adopted,
either exactly or with slight modifications. Following
the teachings of this document he would choose a native
cell line which could be transformed by his oncogene,
and compare the effect of the inhibitors to be screened
on the transformed cell line compared to the native one. If he were lucky enough to have a temperature sensitive variant of his oncogene product, he could make screening easier by comparing the effects of the inhibitor at a temperature where normally the morphological effect was observable, and a second temperature where it was not observable. But even if such a temperature variant were not available, document A58 tells the skilled person what to do to check that any effect is attributable to the interaction of the inhibitor and the protein/gene product of interest, namely to check the effect on the native untransformed line against that on the transformed line, as document A58 does as a precaution on the already found inhibitor oxanosine.

32. Applying the method of document A58 in an obvious manner to other oncogene products to find inhibitors thereto would inevitably lead the skilled person to operate within the area of claim. This claim thus does not meet the requirements of Article 56 EPC, and so the sole request is not allowable and the patent must be revoked.

33. Once the Board has concluded that for the field of oncogenes and their protein products the claimed method is obvious, it is irrelevant that the patentee may have been the first to suggest that the method claimed could be of general application. Every part of the claimed area must meet the requirements for inventive step. Merely because a method is claimed in terms of broader applicability than anything discussed in the prior art, does not mean that the method can be claimed as such, rather the method would need to be confined to non-
obvious applications for which the patent is also enabling, if any such applications exist.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey