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DECISION
of 27 October 2004

Case Number: T 0609/02 - 3.3.8

Application Number: 91917435.9

Publication Number: 0552202

IPC: G01N 33/74

Language of the proceedings: EN

Title of invention:

Methods mediated by the proto-oncogenic protein complex AP-1

Patentee:

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES

Opponents:

Karo Bio AB
Astra AB

Headword:

AP-1 complex/SALT INSTITUTE

Relevant legal provisions:

EPC Art. 83

Keyword:

"Sufficiency of disclosure - no"

Decisions cited:

T 0409/91, G 0009/92, G 0005/83, G 0002/88, G 0006/88,
T 0158/96, T 0241/95

Catchword:

If the description of a patent specification provides no more than a vague indication of a possible medical use for a chemical compound yet to be identified, later more detailed evidence cannot be used to remedy the fundamental insufficiency of disclosure of such subject-matter.



Case Number: T 0609/02 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 27 October 2004

Appellant: THE SALK INSTITUTE FOR BIOLOGICAL STUDIES
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
12 April 2002 concerning maintenance of
European patent No. 0552202 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
M. B. Günzel

Summary of Facts and Submissions

- I. European patent No. 0 552 202 with the title "Methods mediated by the proto-oncogenic protein complex AP-1" was granted with 24 claims for all designated Contracting States except ES and GR and 24 claims for ES and GR on the basis of the international application No. PCT/US91/06848, published as WO 92/05447.
- II. Two oppositions were filed relying on the grounds in Article 100(a) and (b) EPC. In its interlocutory decision dated 12 April 2002, the Opposition Division found that the main request then on file (claims 1 to 7) could not be allowed for the reason that the patent specification did not provide an enabling disclosure in relation to claim 6 (corresponding to granted claim 10) which read as follows:

"6. The use of a compound as identified by the method of claims 1 to 5 for the preparation of a pharmaceutical against over-expression of steroid hormone-responsive or steroid hormone-like compound-responsive gene(s)."

However, the patent was maintained on the basis of the first auxiliary request comprising claims 1 to 5 and 7 of the main request. Claim 1 read as follows:

"1. A method for identifying compound(s) useful for treating abnormal cells, said method comprising selecting a compound which displays both:

- (a) the ability to disrupt the function of AP-1, when said compound is employed in a first assay system comprising a cell line capable of expressing:
 - (i) steroid hormone or steroid hormone-like receptor,
 - (ii) AP-1, and
 - (iii) AP-1-responsive reporter; and

- (b) substantially no ability to promote transcriptional activation of steroid hormone or steroid hormone-like responsive genes, when said compound is employed in a second assay system comprising a cell line capable of expressing:
 - (i) steroid hormone or steroid hormone-like receptor, and
 - (ii) steroid hormone- or steroid hormone-like-responsive reporter."

Dependent claims 2 and 3 related to further features of the method of claim 1. Independent claim 4 was directed to a method for identifying compound(s) which disrupt the AP-1 response pathway, but which exert substantially no effect on steroid hormone or steroid hormone-like responsive pathways. Dependent claim 5 related to further features of the method of claim 4. Independent claim 6 was directed to a method for selecting a compound useful for treating abnormal cells, said method comprising selecting a compound which disrupts the function of AP-1, but has

- substantially no effect on the transcriptional activation of steroid hormone-responsive or steroid hormone-like-responsive genes.
- III. The appellant (patentee) filed a notice of appeal against this decision, paid the appeal fee and submitted a statement of grounds of appeal together with a new main request.
- IV. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of appeal, indicating its preliminary non-binding opinion.
- V. On 27 September 2004, the appellant filed further written submissions together with a new main request and an auxiliary request.
- VI. The respondents (opponents 1 and 2) did not make any written submissions. They did not take part in the oral proceedings although they had been duly summoned.
- VII. At the oral proceedings which took place on 27 October 2004, the appellant filed a new request in replacement of all requests on file. This request comprised claims 1 to 5 and 7 corresponding to claims 1 to 6 which had been accepted by the opposition division (identical to claims 1 to 5 and 7 of the main request filed on 27 September 2004) as well as a claim 6 which read as follows:
- "6. The use of a steroid hormone or steroid hormone analogue as identified by the method of claims 1 to 5, which fails to promote transcriptional activation of glucocorticoid receptor or retinoic acid receptor

genes, for the preparation of a pharmaceutical for the treatment of AP-1 stimulated tumor formation, arthritis, asthma, allergies and rashes."

VIII. The following documents are referred to in the present decision:

OD19: Nagpal, S. et al., The Journal of Biological Chemistry, Vol. 270, No. 2, pages 923 to 927, 1995;

OD22: Fanjul, A. et al., Nature, Vol. 372, pages 107 to 111, November 1994 ;

OD23: Chen, J-Y., The EMBO Journal, Vol. 14, No. 6, pages 1187 to 1197, 1995.

IX. The appellant's arguments may be summarized as follows:

Article 83 EPC; sufficiency of disclosure; claim 6

No difficulties would be encountered when putting the claimed invention into practice.

- On the basis of common general knowledge, the skilled person would be aware of which steroid hormones would be likely to interact with the glucocorticoid or retinoic receptors. Testing the hormones by the method of claim 1 would enable the identification without undue burden of those amongst them having the required properties:

- failing to activate transcription of glucocorticoid or retinoic receptor responsive genes.

- disrupting the AP-1 stimulation of AP-1 responsive genes.

Indeed, it had been acknowledged by the first instance that the patent specification provided sufficient information for the method of claim 1 to be reproduced and these findings had not been challenged on appeal by the opponents.

Post-published state of the art (eg. OD19, OD22, OD23) provided evidence that the methods of the present claims were easily reproducible and led to the identification of compounds that would be appropriate for the use of claim 6.

- Once a steroid hormone with the relevant properties had been identified, it was only a matter to use it. Formulating it as a pharmaceutical composition could be done as a matter of routine. Diseases against which it might be useful were listed in the patent in suit. At the effective date, the skilled person would not doubt that the pharmaceutical would have a therapeutic effect because those diseases were known to be the results of the AP-1 stimulation of certain genes and the patent in suit disclosed that the active ingredient in the pharmaceutical would disrupt this stimulation.

The quoted post-published state of the art as above mentioned clearly established the link between the

steroid hormone as identified in the patent in suit and a disruption of AP-1 stimulation of transcription and it also confirmed that the diseases listed in the patent in suit were likely to be treated by said steroid hormone.

In conclusion, the patent provided sufficient information for the skilled person to be able to reproduce the claimed use in spite of the fact that no technical evidence was given relative to said use, because he/she would necessarily achieve this use by following said information, as was confirmed by the later publications. The requirements of Article 83 EPC were fulfilled in relation to the subject-matter of claim 6.

- X. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 5 and 7 of the main request filed on 27 September 2004 and of claim 6 filed during the oral proceedings on 27 October 2004.

Reasons for the Decision

1. Claims 1 to 5 and 7 of the request for consideration by the board are identical to claim 1 to 6 on the basis of which the opposition division maintained the patent. The patent proprietor is the sole appellant. Thus, in accordance with the Enlarged Board of Appeal decision G 9/92 (OJ EPO 1994, 875, cf order, item 1), the said claims cannot be challenged.

Only claim 6 of the sole request on file is open to review.

Article 123(2)(3) EPC

2. A basis for the subject-matter of claim 6 is found in the application as filed, from line 32 on page 13 to line 28 on page 14. The scope of the claimed subject-matter is narrower than that of the corresponding granted claim 10 (sections II and VII, supra) since

- the compound to be used as an active ingredient in the pharmaceutical composition is restricted to a steroid hormone or steroid hormone analogue capable of interacting with the glucocorticoid- or retinoic-receptors, and

- the diseases stimulated by AP-1 which may be treated with said compound are identified in the claim, and

- the molecular mechanism mentioned in the claim is restricted to compounds failing to promote transcription of the genes rather than to compounds against the over expression in general, of said genes.

In the board's judgment, the expression "which fails to promote transcriptional activation of glucocorticoid receptor or retinoic acid receptor genes" is to be understood as meaning "which fails to promote transcriptional activation of glucocorticoid receptor or retinoic acid receptor **responsive** genes". The requirements of Article 123(2)(3) EPC are fulfilled.

Article 83 EPC; sufficiency of disclosure

3. Claim 6 relates to the use of a steroid hormone or analogue thereof which fails to promote transcriptional activation of glucocorticoid receptor- or retinoic acid receptor- responsive genes, for the preparation of a pharmaceutical for the treatment of AP-1 stimulated tumour formation, arthritis, asthma, allergies and rashes, said hormone being identified by the method according to the previous claims. This latter aspect of the claim (ie definition of the hormone in the so-called "reach-through" format) has been debated to some extent during oral proceedings. However, as the aspect of insufficiency in respect of the medical indication prevailed (cf points 4 to 13, *infra*), it is not necessary to deal with the "reach-through" issue in the present decision.

4. The patent specification describes a study of the "interplay" between the steroid hormone/steroid hormone receptor complex regulating the transcription of steroid hormone-responsive genes and the AP-1 protein regulating the transcription of AP-1 responsive genes. It shows that the transcription which is normally activated by the steroid hormone/steroid hormone receptor complex and the transcription which is normally stimulated by AP-1 are respectively down-regulated by AP-1 and by the steroid hormone receptor (negative cross-regulation). The study is essentially carried out using "custom built" constructs comprising a reporter gene, the expression of which reflects the effect of each regulatory protein/protein complex on transcription under various experimental conditions. It is disclosed that the cross-regulation takes place at

- the protein level, involving an interaction between the steroid receptor and AP-1.
5. The patent specification provides no evidence at all relating to the invention in claim 6: no steroid hormone is identified as binding to the hormone receptor in such a way that the so-formed complex will **disrupt** AP-1 stimulated transcription and at the same time **fail to promote** steroid hormone regulated transcription; no data of any kind are presented indicating that such an hormone (if it were identified) could have an impact on any of the listed specific diseases. In fact, in the application as filed, the sole reference to the potential role of the steroid hormone of claim 6 is found in the passage bridging pages 13 and 14: "*The method of the invention can be employed in a variety of ways, e.g., for treating disease states which are stimulated by AP-1. Such disease states include tumor formation (e.g. formation of lymphomas), arthritis, asthma, allergies, rashes, and the like.*". In short, the patent specification is not concerned with giving a technical basis to what is claimed.
6. The appellant provided post-published evidence showing that steroid hormones such as needed to carry out the use according to claim 6 were later structurally identified and that they, indeed, have an effect on AP-1 stimulated transcription. In document OD19 published in 1995, it is mentioned on page 924, right-hand column: "*These results demonstrate that even though these retinoids do not effectively activate gene expression though RAR α (Table I), they still can antagonize the AP1-dependent expression of 84S-CAT*

through RARa in a potent manner." On page 926, right-hand column, it is further stated: "*Thus, the cross-talk between the retinoid and AP1 signal transduction pathways could clearly be manipulated for therapeutic benefit in inflammatory and hyperproliferative diseases, ...*". In document OD22 published in 1994, summary, the following statement is found: "*Here we describe a new class of retinoids that selectively inhibits AP-1 activity but does not activate transcription.*" and on page 110: "*The anti-AP-1-selective retinoids are of particular interest because of their anti-proliferative activity.*" As for document OD23 published in 1995, summary, it discloses that: "*Using retinoic acid receptor (RAR) reporter cells specific for either RARa, **b** or **g**, we have identified synthetic retinoids... Like RA, these synthetic retinoids allow all three RAR types to repress AP1 (c-Jun/c-Fos) activity, demonstrating that the transactivation and transrepression functions of RARs can be dissociated by properly designed ligands.*" and on page 1195, left-hand column: "*Therefore the possibilities of designing "dissociating" ligands for RA nuclear receptors point to new avenues in the prevention and treatment of proliferative diseases"*.

7. On the basis of the disclosures of these post-published documents, it was argued by the appellant that by carrying out the claimed invention, one would necessarily obtain pharmaceutical compositions since it was by following the teachings of the patent in suit that the post-published results had been obtained. Consequently, in the appellant's opinion, sufficiency of disclosure had to be acknowledged.

8. The board cannot share this opinion. Sufficiency of disclosure must be satisfied at the effective date of the patent, ie on the basis of the information in the patent application together with the common general knowledge then available to the skilled person. Acknowledging sufficiency of disclosure on the basis of relevant technical information produced only after this date would lead to granting a patent for a technical teaching which was achieved, and, thus, for an invention which was made, at a date later than the effective date of the patent. The general principle that the extent of monopoly conferred by a patent should correspond to, and be justified by, the technical contribution to the art, has to be kept in mind (eg. decision T 409/91, OJ EPO 1994, 653).
9. Where a therapeutic application is claimed in the form allowed by the Enlarged Board of Appeal in its decision G 5/83 (OJ EPO 1985, 64), ie in the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application, attaining the claimed therapeutic effect is a functional technical feature of the claim (see G 2/88 and G 6/88, OJ EPO 1993, 93 and 114, Headnote III. and point 9 of the reasons, for non-medical applications, see also T 158/96 of 28 October 1998, point 3.1 of the reasons). As a consequence, under Article 83 EPC, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application. It is a well-known fact that proving the suitability of a given compound as an active ingredient in a pharmaceutical composition might require years and very high developmental costs

which will only be borne by the industry if it has some form of protective rights. Nonetheless, variously formulated claims to pharmaceutical products have been granted under the EPC, all through the years. The patent system takes account of the intrinsic difficulties for a compound to be officially certified as a drug by not requiring an absolute proof that the compound is approved as a drug before it may be claimed as such. The boards of appeal have accepted that for a sufficient disclosure of a therapeutic application, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement in a patent specification that compound X may be used to treat disease Y is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical. It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application (T 241/95, OJ EPO 2001, 103, point 4.1.2 of the reasons, see also T 158/96 of 28 October 1998, point 3.5.2 of the reasons) or, as decision T 158/96 also put it, if there is a "clear and accepted established relationship" between the shown physiological activities and the disease (loc. cit.). Once this evidence is available from the patent application, then post-published (so-called) expert evidence (if any) may be taken into account, but only

to back-up the findings in the patent application in relation to the use of the ingredient as a pharmaceutical, and not to establish sufficiency of disclosure on their own.

10. The appellant argued that experimental tests were in fact irrelevant because no prediction could be made on their basis that the observed effect would equally be seen *in vivo*. The board will agree that an *in vitro* effect may not necessarily be reflected *in vivo*, but this does not lessen the usefulness of *in vitro* tests **in general** in relation to sufficiency of disclosure. Indeed, the *in vitro* tests cannot be performed unless the "protagonists" of the test are available. This means that the skilled person is made aware of the structure of the active ingredient proposed for the pharmaceutical composition as well as, in technical terms, of a definite link between the ingredient and the mechanism allegedly involved in the disease state. The presence of a cause/effect relationship is, thus, made plausible. For how incomplete the data might be, they nonetheless go one step further towards disclosing the invention without leaving an undue burden to the reader. In this context, it should be noted that it is on the very same kind of tests (but published some three to four years later) that the appellant based its arguments in favour of sufficiency of disclosure. In any case, the appellant's argument could not justify the recognition of sufficiency of disclosure in relation to a claim to a therapeutic application of a composition when in the specification there exists no evidence at all of its potential effectiveness.

11. Here, a patent on pharmaceutical drugs for the proposed medical conditions having as active ingredient the steroid hormone of claim 6 does not appear to be justified pursuant to Article 83 EPC since at the effective date,

- no such steroid hormone had in fact been identified, with the corollary that a negative effect on AP-1 stimulation of transcription **and** on the transcription of steroid hormone- responsive genes had not been proven,

and, moreover, there was not a shred of evidence that:

- switching off AP-1 activation of transcription by the claimed hormone would not affect the overall metabolism in such a way as to make said hormone unsuitable as a medicament, nor that

- switching off the transcription of all AP-1 responsive genes would have such an effect on the transcription of those AP-1 responsive genes which are involved in the mentioned diseases so as to produce some relief from said diseases.

Otherwise stated, the subject-matter of claim 6 covers limitless and untried downstream developments in relation to yet to be demonstrated molecular mechanisms. In the board's judgment, it amounts to no more than an invitation to set up further research programs for which no guidance is forthcoming.

12. It is accepted that some years after the filing date of the patent in suit, some steroid hormone analogues were

indeed shown to interfere with AP-1 stimulated transcription as required for the steroid hormone of claim 6. To the board, however, it can only mean that it took a few years of research work possibly involving inventive step and, therefore, undue burden, to put the claimed subject-matter into practice ie to structurally identify the relevant product(s) and show a potential effect in therapy. Even then, the corresponding use as a pharmaceutical was suggested rather than shown (see point 6, supra).

13. In summary, sufficiency of disclosure must, in principle, be shown to exist at the effective date of a patent. If the description of the patent specification, like in the present case, provides no more than a vague indication of a possible medical use for a chemical compound yet to be identified, later more detailed evidence cannot be used to remedy the fundamental insufficiency of disclosure of such subject-matter.
14. For these reasons, it is concluded that sufficiency of disclosure fails in respect of the subject-matter of claim 6.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar

The Chairman

A. Wolinski

L. Galligani