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**Datasheet for the decision
of 23 August 2007**

Case Number: T 1642/06 - 3.3.02

Application Number: 01917284.0

Publication Number: 1267875

IPC: A61K 31/495

Language of the proceedings: EN

Title of invention:

Sigma receptor ligands and their medical uses

Applicant:

Spruce, Barbara, et al

Opponent:

-

Headword:

Sigma receptor/SPRUCE BARBARA, et al

Relevant legal provisions:

EPC Art. 54, 83

Keyword:

"Main request - claim 1 - novelty - yes: undisclosed technical effect identifying a new clinical situation"

"Claims 2 and 4 - sufficiency of disclosure yes: plausible model for sufficiency of disclosure"

Decisions cited:

T 0836/01, T 0290/86, T 0062/88, T 0145/88, T 0158/96,
T 0609/02

Catchword:

-



Case Number: T 1642/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 23 August 2007

Appellant:
(Applicant)

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Decision under appeal:

Decision of the Examining Division of the
European Patent Office posted 15 May 2006
refusing European application No. 01917284.0
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
J.-P. Seitz

Summary of Facts and Submissions

- I. European patent application No. 01 917 284.0 was refused by a decision of the Examining Division pronounced on 29 March 2006 on the grounds of non-compliance with Articles 84, 83 and 54 EPC.
- II. The decision was based on claim 1 of the main request and auxiliary requests 1 to 3 filed on 28 February 2006 and claims 1 and 3 of the fourth auxiliary request filed during the oral proceedings before the Examining Division.

Claim 1 of the main request read:

Use of a sigma receptor ligand for the preparation of a medicament for modulating proliferation and/or survival of normal endothelial cells.

Claim 1 of auxiliary request 1 read:

Use of a sigma receptor ligand for the preparation of a medicament for treating cancer by modulating proliferation and/or survival of normal endothelial cells, wherein the sigma receptor ligand is a sigma receptor antagonist which inhibits endothelial cell proliferation and/or survival.

Claims 1, 2 and 4 of auxiliary request 2 read:

1. Use of a sigma receptor ligand for the preparation of a medicament for inhibiting neovascularisation of tumours, by modulating proliferation and/or survival of endothelial cells, wherein the sigma receptor ligand is

a sigma receptor antagonist which inhibits endothelial cell proliferation and/or survival.

2. Use of a sigma receptor ligand for the preparation of a medicament for the treatment of haemangiomas, psoriasis, diabetic retinopathy, endometriosis, cutaneous scarring or venous shunts, by modulating proliferation and/or survival of endothelial cells, wherein the sigma receptor ligand is a sigma receptor antagonist which inhibits endothelial cell proliferation and/or survival.

4. Use of a sigma receptor ligand for the preparation of a medicament for the treatment of coronary artery disease, varicose ulcers, wound healing, ischaemia, to repair damaged or injured tissue or to promote the integration of tissue grafts, by modulating proliferation and/or survival of endothelial cells, wherein the sigma receptor ligand is a sigma receptor agonist which promotes endothelial cell proliferation and/or survival.

Claim 1 of auxiliary request 3 read:

Use of a sigma receptor ligand for the preparation of a medicament for inhibiting neovascularisation of tumours, by modulating proliferation and/or survival of endothelial cells, wherein the sigma receptor ligand is rimcazole (cis-9-[3,5-dimethyl-1-piperazinyl]propyl]carbazole dihydrochloride) or a variant thereof, rimcazole hydrochloride, BD-1047, BO-1063 or IPAG (1-(4-iodophenyl)-3-(2-adamantyl)guanidine, or a pharmaceutically active salt,

ester, amide, hydrate or free acid or base of any one of said compounds.

Auxiliary request 4 corresponds to auxiliary request 2 with the deletion of claim 1 and consequent renumbering of the claims.

III. According to the decision under appeal, the Examining Division was of the opinion that the subject-matter of claim 1 of the main request and of auxiliary requests 1 to 3 did not fulfil the requirements of Article 54 EPC and that moreover claim 1 of the main request did not fulfil the requirements of Article 84 EPC. As to auxiliary request 4, it considered that claims 1 and 3 did not fulfil the requirements of Article 83 EPC.

The Examining Division considered that the example on page 58, line 10ff of document (1) (WO 00/00599) anticipated the subject-matter of claim 1 of the main request and of auxiliary requests 1 to 3, since it disclosed the treatment of breast cancer using the sigma receptor ligand rimcazole, namely a medical indication covered by said claim. It was of the opinion that the present case related to the mere discovery of a mechanism of action not based on a new technical effect, which, contrary to T 836/01 and T 290/86 (OJ EPO 1992, 414) did not lead to new applications. It also argued that, although G 2/88 (OJ EPO 1990, 93) was not applicable in the present case because this decision relates to a second non-medical use, the reasoning therein nevertheless confirmed the Examining Division's view.

The Examining Division moreover held that the subject-matter of claim 1 of the main request contravened the requirements of Article 84 EPC because, in its view, the definition of a medical indication in terms of a mechanism was not clear.

Claims 1 and 3 of auxiliary request 4 were rejected on the ground of insufficiency of disclosure because, according to the Examining Division, there was no evidence in the application that sigma receptor agonists and antagonists were useful in the treatment of the various diseases listed in these two claims.

Accordingly, all requests were rejected.

IV. The appellant (applicant) lodged an appeal against this decision.

It filed a main request and auxiliary requests 1 to 3 with its grounds of appeal.

Claim 1 of the main request is identical to claim 1 of auxiliary request 2 dealt with by the Examining Division in its decision and claims 2 and 4 of this request are identical to claims 1 and 3 of auxiliary request 4 dealt with by the Examining Division in its decision.

V. Oral proceedings were held on 23 August 2007.

VI. The arguments submitted by the Appellant can be summarised as follows:

The invention lay in the identification of a new technical effect, namely the use of sigma ligands to modulate the proliferation or survival of endothelial cells. Based on this undisclosed technical effect, the claimed subject-matter was novel.

As to the objection of insufficiency of disclosure, the results in the application demonstrating the angiogenesis modulating effects of sigma ligands reflected the claimed therapeutic application of claims 2 and 4, so that the application provided sufficient evidence of the therapeutic applications in accordance with the case law.

VII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or, subsidiarily of either of auxiliary requests 1 to 3 filed with letter dated 25 September 2006.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request*

2.1 Claim 1

Article 54 EPC

2.1.1 Document (1) is the only document considered by the Examining Division against novelty of the subject-matter of said claim.

This document discloses the use of a sigma receptor ligand (rimacazole) for the preparation of a medicament for treating tumors (breast cancer) (see examples page 58, lines 10 to page 60, line 12).

Since document (1) and claim 1 are both concerned with the same composition for treating the same disease, it has therefore to be decided whether the now claimed use represents further and different therapeutic use from that disclosed in document (1).

Document (1) discloses the use of compositions for the purpose of inducing tumour cell division cycle arrest and/or apoptosis (see e.g., claim 1). Thus, document (1) teaches a **direct** effect on cancer cells. This is in clear contrast to the technical effect relied upon in claim 1, namely the **indirect** influence of sigma receptor ligands on tumour cells via the inhibition of the neovascularisation of tumours.

This effect, moreover, identifies a new clinical situation, namely one in which it could be preferable to target the supporting vasculature of a tumour rather than the cancer cells themselves, for instance in cases where the cells are resistant to chemotherapeutic drugs.

In view of the foregoing, the Board is satisfied that the subject-matter of claim 1 at issue fulfils the requirements of Article 54(2) EPC vis-à-vis document (1).

2.1.2 On the basis of the above, the Board does not share the Examining Division's view that the subject-matter of claim 1 relates merely to the discovery of a new mechanism of action devoid of new applications, contrary to T 836/01 and T 290/86.

T 836/01 reflects in fact the same situation as in the present case. The Board accepted in that case that claims directed to the use of IL-6 to **directly** influence tumour growth and differentiation were novel over a prior art disclosure of the use of IL-6 to **indirectly** treat cancer by activating T cells, i.e. the Board held that a new technical effect resided in the medical indication of the treatment of cancer vs. enhancement of the immune system (see reasons, 7 and 10).

In T 290/86 the situation is again directly comparable with the present case. The claims in T 290/86 were directed to the use of lanthanum salts to remove plaque, which would have the effect inter alia of inhibiting tooth decay. In the present case, claim 1 of the main request is directed to the use of sigma ligands to inhibit tumour neovascularisation, which would have the effect inter alia of treating cancer. The prior art in T 290/86 disclosed the use of lanthanum salts to reduce the solubility of tooth enamel, which would inhibit tooth decay. The prior art in the present case discloses the use of sigma ligands to inhibit tumour cell survival, which would treat cancer. The overlap in the therapeutic application of the use of the prior art and the use of the claim is irrelevant, because the technical effect stated in the

claim identifies a new clinical situation and remains different from that of the prior art.

As to G 2/88, the Board observe that it relates to second use in general (see Reasons, 6.1: "In contrast, the question of law which has been referred to the Enlarged Board is not related to medical inventions but is of a general nature, being primarily concerned with the question of interpretation of Article 54(1) and (2) EPC"). Accordingly, the interpretation of Article 54(1) and (2) made by the Enlarged Board in G 2/88 applies in all cases.

It is true, as mentioned by the Examining Division in its decision, that G 2/88 applies only to the use of "a known entity for a new purpose". But it is not correct to contend that it could not apply to the present situation only because the purpose is the same as that dealt with by the prior art, i.e. the treatment of cancer. Otherwise, such a construction would completely ignore the fact that the "new purpose" of the present invention as defined in claim 1 is the inhibition of tumour angiogenesis, and that this use is not disclosed as such in the prior art.

Thus, the case law cited in the Examining Division's decision clearly supports the argument that claim 1 represents a new technical effect and is thus novel over the prior art.

2.2 Claims 2 and 4

Article 83 EPC

These claims were rejected by the Examining Division on the ground of insufficiency of disclosure.

In its decision, the Examining Division asserted that the applicant had not demonstrated a therapeutic effect when sigma receptor antagonists or agonists are applied to the therapeutic indications recited in claims 2 and 4 and that the specification provided no evidence that sigma ligands can be used to treat any disease other than cancer.

In that respect, the Board notes that, according to EPO case law and practice (see e.g. T 145/98 (reasons 8), T 158/96 (reasons, 3.5.2), T 609/02 (reasons, 9)), in order for a second medical use claim to be deemed supported, it is not necessary for a therapeutic effect to have been demonstrated clinically. Rather, the determinative factor for a finding of such support is that, for the skilled person, the effect shown in the application for the substance (for example, a pharmacological or pharmaceutical effect or an effect observed *in vitro* models or on animal models) directly and unambiguously reflects the claimed therapeutic applications, i.e. that the skilled person understands on the basis of generally accepted models that the results in the application directly and unambiguously reflect the claimed therapeutic applications.

This is in fact the situation where, in the present case, in addition to the multiple examples showing that sigma ligand antagonists inhibit endothelial cell growth and proliferation (see pages 34-35 and 41-43), the specification shows that sigma ligand antagonists inhibit angiogenesis in vitro and in vivo (page 36 and 37-38).

This has not been contested by the Examining Division.

The specification also shows that sigma ligand agonists have a stimulatory effect on endothelial cell proliferation and/or survival (see below). The specification thus provides ample evidence of the modulating effects of sigma ligand antagonists and agonists on endothelial cell growth and proliferation and angiogenesis.

The only objection made in the Examining Division's decision related to the experiments described in the specification at page 51 which, in the Examining Division's opinion, did not provide sufficient evidence to show that sigma agonists have the opposite effects to those of sigma antagonists, as the sigma agonists and antagonists were used together.

However, the Board observes that this is not the only evidence for the effect of sigma agonists provided in the specification. For example, Table 1 (page 54) shows a clear stimulatory effect of sigma-1 agonists (+)-pentazocine and (+)-SKF-10,047, namely that: values of 110% and 120% denote viable cell numbers that are higher after exposure to agonists for 4 days than control cell numbers (100%) in untreated cell

populations. This indicates a stimulatory effect of sigma-1 agonists on endothelial cell proliferation and/or survival. Furthermore, Figure 3 in the specification shows survival activity greater than 100% in endothelial cells exposed to (+)-pentazocine (Pent 4 μ M) alone.

Thus, the application provides evidence of the effects of sigma agonists administered alone, which was presumably not considered by the Examining Division.

Moreover, the person skilled in the present art is well aware of the involvement of angiogenesis in many diseases and conditions and the potential of angiogenesis modulators to treat such diseases and conditions is generally accepted in the art.

The Examining Division did not provide any elements to show that angiogenesis is not involved in the applications cited in claims 2 and 4 and the Board has no reason to doubt such involvement.

Accordingly, in the absence of any **concrete** evidence to the contrary the Board concludes that, as the facts on file stand, the requirements of sufficiency of disclosure under Article 83 EPC have been fulfilled **but only as far as** the medical indications in claims 2 and 4 are concerned. A complete examination under Article 83 EPC has yet to be performed.

3. *Remittal*

It follows from the above that the subject-matter of claim 1 of the main request fulfils the requirements of

Article 54 EPC vis-à-vis document (1) and that the medical indications of claims 2 and 4 must be considered as **plausible** in the light of the facts as they stand.

The Board cannot, however, take a decision on the case as a whole since the decision under appeal was based solely on deficiencies of claim 1 with respect to Articles 54 vis-à-vis document (1) and of claims 2 and 4 with respect to Article 83 EPC and only as far as the medical indications were concerned. It is noted that the Examining Division has not yet ruled on the other requirements for granting a European patent, and these issues clearly require careful consideration, in particular having regard to the novelty assessment discussed under 2.1 above and the functional definition of "a ligand" given in the claims.

In the light of the above findings, it is necessary to remit the case to the first instance for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance for further prosecution.

The Registrar

The Chairman

A. Townend

U. Oswald