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**Datasheet for the decision  
of 28 September 2011**

**Case Number:** T 0626/08 - 3.3.02

**Application Number:** 01952097.2

**Publication Number:** 1401438

**IPC:** A61K 31/4355, A61P 35/00

**Language of the proceedings:** EN

**Title of invention:**

Use of cyclopamine in the treatment of basal cell carcinoma  
and other tumors

**Patentee:**

Tas, Sinan

**Opponent:**

Curis , Inc.

**Headword:**

Cyclopamine in the treatment of BCC/TAS SINAN

**Relevant legal provisions:**

EPC Art. 123(2)

**Relevant legal provisions (EPC 1973):**

-

**Keyword:**

"All requests: Article 123(2) - (no): unallowable  
generalisation"

**Decisions cited:**

G 0001/03

**Catchword:**

-



Case Number: T 0626/08 - 3.3.02

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.02  
of 28 September 2011

**Appellant:** Tas, Sinan  
(Applicant) S.H. Tuncel Caddesi No. 36  
Ahmet Kuddusi Mahallesi  
Bor 51700 (TR)

**Representative:** -

**Respondent:** Curis, Inc.  
(Opponent) 61 Moulton Street  
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**Representative:** von Uexküll - Gülденband, Alexa  
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**Decision under appeal:** Decision of the Opposition Division of the  
European Patent Office posted 14 March 2008  
revoking European patent No. 1401438 pursuant  
to Article 101(3)(b) EPC.

**Composition of the Board:**

**Chairman:** U. Oswald  
**Members:** A. Lindner  
R. Cramer

## Summary of Facts and Submissions

- I. European patent No. 1 401 438 based on application No. 01 952 097.2 was granted on the basis of 9 claims. The sole independent claim reads as follows:
- "1. Use of cyclopamine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for obtaining decreased size or disappearance of a tumor employing hedgehog/smoothened signalling for the prevention of apoptosis and/or for the prevention of differentiation of tumor cells, wherein said medicament is to be administered in an amount which induces differentiation and apoptosis of said tumor cells."
- II. An opposition was filed against the patent. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step and under Article 100(c) EPC for amendments that contained subject-matter extending beyond the content of the application as originally filed.
- III. The documents cited during the opposition and appeal proceedings included the following:
- (1) WO 99/52534
  - (32) Genes & Development 19, 214-223 (2005).
- IV. In the decision pronounced on 14 February 2008 and posted on 14 March 2008, the opposition division revoked the European patent pursuant to Article 101(3)(b) EPC.

V. Regarding the main request, the opposition division concluded that the feature "decreased size" was not mentioned in the original application and that the feature "disappearance of a tumor" was disclosed only in connection with basal cell carcinoma (BCC). As a consequence, the requirements of Article 123(2) EPC were not met. The subject-matter of auxiliary request 1 was found not to meet the requirements of Article 123(2) EPC, as the skilled person could not directly and unambiguously derive from the original application that treatment with cyclopamine resulted in a decreased size or disappearance of tumors using the hedgehog/smoothened pathway for proliferation and prevention of apoptosis.

The opposition division came to the conclusion that auxiliary requests 2 and 3 were allowable under Article 123(2) EPC. However, none of auxiliary requests 2 and 3 met the requirements of Article 54 EPC, as the subject-matter claimed therein was not novel over document (1).

VI. The patentee (appellant) lodged an appeal against that decision.

VII. With the statement of the grounds of appeal dated 17 July 2008, the appellant filed a main request and auxiliary requests 1 to 3. The sole independent claims of auxiliary requests 1 to 3 read as follows:

*(i) Auxiliary request 1:*

"1. Use of cyclopamine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for

obtaining decreased size or disappearance of a tumor employing hedgehog/smoothened signaling for the prevention of apoptosis and/or for the prevention of differentiation of tumor cells, wherein said medicament is to be administered in a dose which induces differentiation and apoptosis of said tumor cells."

*(ii) Auxiliary request 2:*

"1. Use of cyclopamine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for obtaining decreased size or disappearance of a tumor employing hedgehog/smoothened signaling for the prevention of apoptosis and/or for the prevention of differentiation of tumor cells, wherein said medicament is to be administered in a dose which induces differentiation and apoptosis of said tumor cells to cause decreased size or disappearance of said tumor."

*(iii) Auxiliary request 3:*

"1. Use of cyclopamine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treatment of basal cell carcinoma for obtaining decreased size or disappearance of a tumor employing hedgehog/smoothened signaling for the prevention of apoptosis and/or for the prevention of differentiation of tumor cells, wherein said medicament is to be administered in an amount which induces differentiation and apoptosis of said tumor cells."

VIII. Oral proceedings were held before the board on 28 September 2011.

IX. The appellant's arguments in connection with the ground of opposition according to Article 100(c) EPC can be summarised as follows:

Regarding the feature "for obtaining decreased size or disappearance of a tumor", it was argued that the teaching of the original application was not limited to BCC's but included all types of tumors using the *hedgehog/signalling* pathway. As the original application provided the scientific basis for the successful treatment of all these tumors by administration of cyclopramine, the skilled person would know that the invention, which had been exemplified by treating BCC's, could be extended to all the tumors mentioned above. Thus, the passages on page 1, lines 8-14 and page 6, lines 12-16 clearly stated that cyclopramine was not limited to the treatment of BCC's but could also be used for the treatment of other tumors using the *hedgehog/signalling* pathway. Furthermore, there was an explicit disclosure for the feature "decreased size" on page 3, lines 19-20 of the original application mentioning "rapid clinical regressions of the BCC's", which were also shown in figures 1A to 1D. In addition, there were further passages in the original application, e.g. on page 3, lines 23-27 and page 7, lines 2-6, illustrating that administration of cyclopramine effected a decrease in tumor size. As the original application showed that disappearance of the treated BCC nodules was caused by massive apoptotic activity, the skilled person clearly understood that the treatment described in the original application was directed to and effective on any tumor using the *hedgehog/signalling* pathway. Furthermore, the original application was not limited to topical

administration but also included systemic administration, which meant that internal tumors using the *hedgehog/signalling* pathway could be treated as well.

- X. In connection with the ground of opposition according to Article 100(c) EPC, the respondent argued that the features "for obtaining decreased size or disappearance of a tumor" and "wherein said medicament is to be administered in an amount which induces differentiation and apoptosis of said tumor cells" of claim 1 as granted of the main request had no basis in the original application. These objections also applied to each claim 1 of auxiliary requests 1 to 3, which were not allowable under Article 123(2) EPC.
  
- XI. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims as granted (main request), or alternatively, on the basis of the auxiliary requests 1 to 3 filed with the grounds of appeal.
  
- XII. The respondent requested that the appeal be dismissed.

### **Reasons for the Decision**

- 1. The appeal is admissible.
  
- 2. Main request - amendments:
  - 2.1 Basis for the feature "for obtaining decreased size of a tumor" in the original application

As was correctly pointed out in decision under appeal (see point II.2.1.1 of the reasons for the decision), the term "decreased size" does not appear in the original application. However, the original application mentions "clinical regressions of the BCC's" (see page 3, line 19) and "Rapid regressions of the cyclopamine-treated BCC's" (page 7, line 2). It therefore has to be examined whether or not these two expressions are equivalent. In contrast to the evaluation of the opposition division (see point II.4.2.4 of the reasons for the decision), the board is of the opinion that the term "decreased size of said tumor" is limited to a real decrease in size, i.e. a decrease in size as compared to its size at the beginning of the treatment. As a consequence, "decrease in size" is equivalent to "regression". As a next step, it has to be evaluated whether the clinical regressions of the BCC's can be generalised to obtaining decreased size of all tumors employing hedgehog/smoothened signaling for the prevention of apoptosis and/or for the prevention of differentiation of tumor cells as claimed in claim 1 of the main request. Article 123(2) EPC stipulates that the European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. According to the established jurisprudence of the boards of appeal, this content only encompasses what can be directly and unambiguously deduced from the explicit and implicit disclosure of the application as filed. In this context, the board wants to emphasise the importance of applying a uniform concept of disclosure for the purposes of Articles 54, 87 and 123(2) EPC (see 4th paragraph of point 2.2.2 of G 1/03 (OJ EPO 2004, 413), which means that an amendment must not create novel



subject-matter. The first paragraph of the original application discloses the "use of cyclopamine ... in the treatment of BCC's and other tumors that use the *hedgehog/smoothened* signal transduction pathway for proliferation and prevention of apoptosis." A similar disclosure can be found in the last paragraph of page 6, which mentions "the use of cyclopamine not only on BCC's but also on those internal tumors that utilise the *hedgehog/smoothened* pathway for proliferation and for prevention of apoptosis and/or differentiation." It follows therefrom that there is a basis for the use of cyclopramine for the treatment of all tumors using the *hedgehog/smoothened* signal transduction pathway for proliferation and prevention of apoptosis. However, such a treatment, even if it is successful, does not necessarily result in a decreased size of the tumor which was disclosed only in connection with BCC's (see page 3, lines 19-22 and page 7, lines 1-6 of the original application). The original application mentions on page 1, lines 8-9 that "causation of apoptosis by cyclopamine is by a non-genotoxic mechanism" which according to the reasoning of the appellant provides a basis for the feature for obtaining decreased size for every tumor employing hedgehog/smoothened signalling, as apoptosis, which means cell death, inevitably leads to tumor shrinkage.

The board cannot follow this argumentation because a decrease of the tumor size occurs only if the overall rate of apoptosis is superior to the overall proliferation rate of tumor cells not affected by apoptosis. As there is no indication that this would inevitably be the case, the feature "for obtaining decreased size of a tumor employing hedgehog/smoothened

signalling for the prevention of apoptosis and/or for the prevention of differentiation of tumor cells" is not supported by the feature "clinical regressions of the BCC's" and has therefore no basis in the original application. Document (32), cited by the appellant in this context, also concerns the treatment of BCC's and is therefore not pertinent for this issue.

2.2 Basis for the feature "for obtaining disappearance of a tumor" in the original application

2.2.1 The passage on page 3, lines 19-22 of the original application, which makes reference to figures 1A - 1D, which also concern the treatment of BCC's, mentions the "visual disappearance of several tumor areas." This passage does not provide a basis for the above-mentioned feature, because (a) the visual disappearance of several tumor areas is not equivalent to the disappearance of the tumor *in toto*, and (b) said passage also concerns BCC's, which cannot be directly and unambiguously generalised to any tumor employing hedgehog/smoothened signalling for the prevention of apoptosis and/or for the prevention of differentiation of tumor cells.

2.2.2 According to page 4, lines 1-3 of the original application, figure 2A and 2B show the skin areas corresponding to the visually disappeared tumor nodules. Furthermore, the tumors are seen to have disappeared to leave behind large cystic structures containing little material inside and no detectable tumor cells. This passage does not provide a basis for the above-mentioned feature, because (a) the figures in question relate to a method of treatment comprising surgical

excisions in combination with administration of cyclopamine (see page 3, lines 23-27), which cannot be directly and unambiguously extended to treatment with cyclopamine without surgery and (b) said passage also concerns BCC's, which cannot be directly and unambiguously generalised to any tumor employing hedgehog/smoothened signalling for the prevention of apoptosis and/or for the prevention of differentiation of tumor cells either.

- 2.3 For all these reasons, the subject-matter of claim 1 of the main request does not meet the requirements of Article 123(2) EPC.

3. Auxiliary request 1 - amendments

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in that the feature "in an amount" has been replaced by "in a dose". This modification is not suitable for overcoming the objections raised above in points 2.1 and 2.2 in connection with the main request, which therefore apply *mutatis muntandis* to claim 1 of auxiliary request 1. As a consequence, the requirements of Article 123(2) EPC are not met.

4. Auxiliary request 2 - amendments

Claim 1 of auxiliary request 2 differs from claim 1 of the main request by the replacement of the feature "in an amount" by "in a dose" and by addition of "to cause decreased size or disappearance of said tumor" at the end of the claim. Both modifications are not suitable for overcoming the objections raised above in points 2.1 and 2.2 in connection with the main request, which

therefore apply *mutatis muntandis* to claim 1 of auxiliary request 2. As a consequence, the requirements of Article 123(2) EPC are not met.

5. Auxiliary request 3 - amendments

Claim 1 of auxiliary request 3 differs from claim 1 of the main request in that the treatment is limited to BCC's. The board notes that the objections raised in point 2.1 above have been overcome by this amendment. In this context, it is emphasised that the board cannot follow the respondent's argument according to which the feature "clinical regressions of the BCC's" (see page 3, line 19 of the original application), which serves as the basis for the feature "decreased size" (see first paragraph of point 2.1 above), was disclosed in the original application only in conjunction with topical administration, in view of the disclosure on page 3, lines 15-18 of the original application, which indicates that other modes of administration are foreseen.

However, the objections raised in points 2.2.1, item (a) (the visual disappearance of several tumor areas is not equivalent to the disappearance of the tumor *in toto*) and 2.2.2, item (a) (the figures in question relate to a method of treatment comprising surgical excisions in combination with administration of cyclopamine (see page 3, lines 23-27), which cannot be directly and unambiguously extended to treatment with cyclopamine without surgery) are addressed to all tumors including BCC's. As a consequence, there is no basis in the original application for the feature "for treatment of basal cell carcinoma for obtaining ...

disappearance of a tumor...". As a consequence, the subject-matter of claim 1 of auxiliary request 3 is not allowable under Article 123(2) EPC.

6. In view of these findings, an evaluation of the further grounds of opposition and further objections raised by the respondent is not necessary.

## **Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman:

N. Maslin

U. Oswald