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# Datasheet for the decision of 27 August 2014

**Case Number:** T 1616/09 - 3.3.02

**Application Number:** 02717415.0

**Publication Number:** 1383379

**IPC:** A61K45/00, A61P35/00

**Language of the proceedings:** EN

**Title of invention:**
RESTORATION OF CANCER-SUPPRESSING FUNCTIONS TO NEOPLASTIC CELLS THROUGH DNA HYPOMETHYLATION

**Applicant:**
SuperGen, Inc.

**Headword:**
Combination therapy with anti-neoplastic agent and DNA methylation inhibitor/SUPERGEN

**Relevant legal provisions:**
EPC Art. 83, 111(1)
EPC R. 42(1)(e)

**Keyword:**
Sufficiency of disclosure - (yes)
Remittal to the department of first instance (yes)

**Decisions cited:**
T 0609/02

**Catchword:**

For the purposes of Article 83 EPC, the level of disclosure in the application which is required for claims directed to pharmaceutical compositions or kits is not the same as that which is required for medical-use claims. For claims directed to pharmaceutical compositions or kits it is in principle sufficient that the application provides information which allows the skilled person to produce the composition or kit, and that there are no substantiated doubts that it could indeed be used in therapy. For second-medical-use claims on the other hand it is required not only that the composition itself is disclosed in an enabling way but also that its suitability for the claimed treatment is plausibly disclosed in the application (Reasons 6).

In the case of a claim directed to a pharmaceutical composition comprising two classes of compounds which have both already been used in therapy in the prior art, there is a priori no reason to doubt that such a pharmaceutical composition can be produced; no specific functional effect has to be demonstrated (Reasons 6.1.1 and 6.1.2).

In the case of second-medical-use claims, if the claimed therapeutic effect was already known to the skilled person at the priority date, it is not necessary to demonstrate it in the application (Reasons 6.2.2).

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**Case Number: T 1616/09 - 3.3.02**

# D E C I S I O N
# of Technical Board of Appeal 3.3.02
# of 27 August 2014

| | |
|---|---|
| **Appellant:** (Applicant) | SuperGen, Inc.<br>4141 Dublin Boulevard, Suite 200<br>Dublin, California 94568 (US) |
| **Representative:** | Crooks, Elizabeth Caroline<br>Kilburn & Strode LLP<br>20 Red Lion Street<br>London WC1R 4PJ (GB) |
| **Decision under appeal:** | **Decision of the Examining Division of the European Patent Office posted on 1 April 2009 refusing European patent application No. 02717415.0 pursuant to Article 97(2) EPC.** |

**Composition of the Board:**

**Chairman:** U. Oswald
**Members:** T. Sommerfeld
S. Fernández de Córdoba

## Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division, pronounced on 20 February 2009 and posted on 1 April 2009, in which European patent application 02717415.0, based on the international application published as WO 02/067681, was refused under Article 97(2) EPC.

II. The documents cited in the examination and appeal proceedings include the following:

D2.1 Valeriote F. and Lin H., Cancer Chemotherapy Reports 1975; 59 (5), 895-900
D3.1 Beltran A. et al, Mol. Cancer Ther. 2008; 7(5), 1080-1090
D3.2 Eramo A. et al, Cancer Res. 2005; 65(24), 11469-11477
D3.3 Fang X. et al, Oncol. Reports 2004; 12, 523-526
D4.1 Gollob J. and Sciambi C., Clin. Cancer Res. 2007; 13(17), 5219-5225
D5.10 Appleton K. et al, J. Clin. Oncol. 2007; 25(29), 4603-4609

III. The decision of the examining division is based on the sets of claims of the main request and of auxiliary requests 1 to 3, which were all filed with letter of 19 January 2009.

The set of claims according to the main request comprised 39 claims, of which independent claims 1, 20, 22, 23 and 36 read as follows:

"1. A pharmaceutical composition comprising:
a DNA methylation inhibitor; and

an anti-neoplastic agent whose activity as an anti-neoplastic agent *in vivo* is adversely affected by aberrant DNA methylation."

"20. A combination of a DNA methylation inhibitor and an anti-neoplastic agent whose activity as an anti-neoplastic agent *in vivo* is adversely affected by aberrant DNA methylation, for use in a method of treating a disease associated with abnormal cell proliferation."

"22. Use of a DNA methylation inhibitor for the preparation of a pharmaceutical composition for treatment of a disease associated with abnormal cell proliferation, in which the pharmaceutical composition additionally comprises an anti-neoplastic agent whose activity as an anti-neoplastic agent *in vivo* is adversely affected by aberrant DNA methylation."

"23. Use of an anti-neoplastic agent for the preparation of a pharmaceutical composition for the treatment of a disease associated with abnormal cell proliferation, in which the activity of the anti-neoplastic agent *in vivo* is adversely affected by aberrant DNA methylation, and in which the pharmaceutical composition additionally comprises a DNA methylation inhibitor."

"36. A kit for treating a disease associated with abnormal cell proliferation, comprising:

a container that contains decitabine and an anti-neoplastic agent whose activity as an anti-neoplastic agent *in vivo* is adversely affected by aberrant DNA methylation."

IV. The examining division decided that the description (sic) did not meet the requirements of Rule 42(e) EPC (sic) and Article 83 EPC.

The description stated the problem to be solved as being to improve the effectiveness of antineoplastic agents, and indicated that such improvement could be synergistic. However, the most detailed section of the description, which was on page 19 and related to the combination of the specific DNA methylation inhibitor decitabine and the anti-neoplastic agent cisplatin, failed to give "any test procedure, any enzyme, cell line or animal model, any results, any statistical analysis of those results[,] any indication as to how such results should be regarded as an improvement or synergy". Since D1 (=D2.1 in the present proceedings) indicated "difficulties in showing synergistic effect in the evaluation of two anti neoplastic drugs", in order "to claim any form of improvement or synergy the present description must detail exactly how the Applicant has demonstrated his invention". Moreover, there was no suggestion as to how this "could be generalised (...) to cover the 700 or so listed anti-neoplastic agents in combination with the 80 or so listed neoplastic conditions".

V. The applicant (hereinafter, the appellant) lodged an appeal against the decision of the examining division. With the statement of the grounds of appeal, it requested that the decision be set aside and that the application "be held to satisfy Art 83 on the basis of the Main Request or any of the Auxiliary Requests (1 to 8) contained herein"; oral proceedings were requested as an auxiliary measure. Moreover, the appellant submitted documents D2.1 (D1 before the first instance), D3.1 to D3.3, D4.1 (which had already been

introduced into the first-instance proceedings by the examining division) and D5.1 to D5.10.

The **main request** is identical to the main request which was decided upon by the examining division (see section III above).

VI. With fax dated 8 May 2014, sent in reaction to a communication by the board asking the appellant to clarify its requests, the appellant confirmed that its request was that the decision under appeal be set aside and the case be remitted to the examining division for further prosecution.

VII. The appellant's arguments, in so far as relevant to the present decision, may be summarised as follows:

Document D2.1 was published 26 years before the priority date of the application, and even then it was possible to test for synergistic effects of combinations of cancer drugs. Moreover, the application disclosed a different concept to that of D2.1, since it taught the use of a methylation inhibitor acting on cells to render them more sensitive to an antineoplastic agent: in those cells where aberrant DNA methylation had altered the expression levels of genes whose expression was required for the activity of an anti-neoplastic agent, the methylation inhibitor caused the cells to be able to react to the antineoplastic agent. The methylation inhibitor was selected as a function of a property of the cells rather than because of a synergistic cell-killing effect with an antineoplastic agent. In this context, the application provided at least two examples of such cells with hypermethylation at a particular site (RARβ at page 18, lines 20 to 28 and hMLH-1 at page 19, lines 14 to 24).

Sufficient details concerning the pharmaceutical compositions were given in the application e.g. on page 37, lines 25 to page 38, line 2; page 38, lines 10 to 14; page 38, line 29 to page 39 line 4; the examining division had not provided any reasons why the examples set out in the application would not work. The underlying metabolic mechanism of a number of anti-neoplastic agents and of several DNA methylation inhibitors was well known in the art. Since the physiological basis was not in doubt and clear instructions on how to carry out the invention were given, no examples including results data were required in the application.
Documents D4.1, D3.1, D3.2 and D3.3 confirmed, as post-published evidence, that the effectiveness of the anti-neoplastic agent was enhanced when used according to the invention.
Document D5.10 showed that combinations of an inhibitor and an agent according to the invention had a therapeutic effect.

VIII. The appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division for further prosecution.

## Reasons for the Decision

1. The appeal is admissible.

Main request: Article 83 and Rule 42(1)(e) EPC

2. The examining division objected to the description as not meeting the requirements of Article 83 and Rule 42(1)(e) EPC.

3. Rule 42(1)(e) EPC states that "the description shall describe in detail at least one way of carrying out the invention claimed, using examples where appropriate and referring to the drawings, if any".
Article 83 EPC states that the patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. In other words, the teaching of the application as a whole must enable the skilled person to carry out, without undue burden, the invention which is defined in the claims.

4. In its decision, the examining division referred to the subject-matter not of the claims but of the description. For the purposes of Article 83 EPC as well as of Rule 42(1)(e) EPC, it is the invention, as defined by the claims, which has to be disclosed in the application in an enabling and detailed way.
Examination of whether the description, as part of the application, provides such enablement and detail has thus to be done vis-à-vis the claimed subject-matter.

5. The present main request comprises product claims directed to pharmaceutical compositions (claims 1 to 19), as well as claims directed to medical uses, in the format of either purpose-restricted product claims (claims 20 and 21, and dependent claims) or Swiss-type medical-use claims (claims 22 and 23, and dependent claims), and product claims directed to kits (claims 36 to 39).

6. Clearly the level of disclosure which is required for these different categories of claims is not the same. For example, for claims directed to pharmaceutical compositions or kits - which are product claims, not

restricted to any specific therapeutic effect - it is in principle sufficient that the application provides information which allows the skilled person to produce the composition or kit, and that there are no substantiated doubts that it could indeed be used in therapy. For second medical-use claims on the other hand it is required not only that the composition itself is disclosed in an enabling way but also that its suitability for the claimed treatment is plausibly disclosed in the application.

6.1 Independent claim 1: Pharmaceutical compositions

6.1.1 Claim 1 is directed to a pharmaceutical composition comprising a DNA methylation inhibitor and an anti-neoplastic agent, wherein the anti-neoplastic agent is further defined by a functional feature, namely that its activity is adversely affected by aberrant DNA methylation. As an example of DNA methylation inhibitors, cytidine analogs are mentioned and specifically decitabine (e.g. application page 7, lines 9 to 12), a compound whose use in therapy had already been disclosed in the prior art (e.g. Schwartsmann G. et al., Investigational New Drugs 18: 83-91, 2000, cited in the European search report). The application also provides a long list of available anti-neoplastic agents (page 1, line 15 to page 6, line 21), and further indicates which anti-neoplastic agents are part of the embodiments of the invention (page 7, line 13 to page 9, line 8); examples of combinations comprising specific groups of anti-neoplastic agents are also disclosed on page 17, line 26 to page 29, line 28. There is no reason to doubt that such products could be formulated as pharmaceutical compositions, since they were indeed individually available in the prior art as such and had also been used in combination

(Schwartsmann et al., *supra*). The board thus considers that the application as filed, and in particular the description, contains sufficient information to enable the skilled person to produce the pharmaceutical compositions as claimed.

6.1.2 The arguments of the examining division were based on an alleged lack of evidence in the application showing that the technical problem as stated in the application - synergistic improvement of the effectiveness of anti-neoplastic agents - had indeed been solved, especially in view of all possible anti-neoplastic agents encompassed in the claims. Since enablement of claims conferring absolute protection for products does not require that any specific functional effect be demonstrated, but rather that the product can be produced, this argument fails. The board agrees that claim 1 has very broad limits, but these are well defined and the skilled person would know without undue burden which compounds were encompassed and which were not: all that is required is to test whether or not the anti-neoplastic activity of the anti-neoplastic agent is indeed impaired by aberrant DNA methylation (a phenomenon which is explained in the application e.g. at pages 12 and 13). The examining division has not provided any arguments, let alone substantiated by facts, that such testing would not be possible without undue burden.

6.2 Independent claims 20 to 23: Medical uses

6.2.1 Claims 20 to 23 are directed to medical uses of combinations of a DNA methylation inhibitor and an anti-neoplastic agent, wherein the medical use is for treating a disease associated with abnormal cell proliferation. By definition, attaining the claimed

therapeutic effect is a functional technical feature of claims directed to medical uses. 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 (T 609/02, reasons 9).

6.2.2 As stated above, the therapeutic application as claimed is treatment of a disease associated with abnormal cell proliferation. Undisputedly, anti-neoplastic agents are, by definition, used to treat cancer, which is an example of a disorder associated with abnormal cell proliferation, and aim, either directly or indirectly and via different mechanisms, at controlling such abnormal cell proliferation: this was state of the art for the present application. Hence, even in the absence of any data in the application showing a therapeutic effect of these agents either on cancer or on other diseases associated with abnormal cell proliferation, there is no apparent reason to doubt that anti-neoplastic agents would have a role in controlling abnormal cell proliferation both in cancer and in other diseases not related to cancer. As such, it can be considered that said claimed therapeutic effect was already known to the skilled person at the priority date and that it therefore does not have to be demonstrated in the application. The fact that the compound to be used consists of a combination with a further substance, namely a DNA methylation inhibitor, does not change this conclusion, unless there were reasons, based on verifiable facts, to believe that this substance would interfere in a negative way with the activity of the anti-neoplastic agent. On the contrary, the teaching of the application is that this further compound may enhance the activity of the anti-

neoplastic agent, and this is further supported by the post-published evidence submitted by the appellant with the grounds of appeal (documents D3.1, D3.2, D3.3, D5.10).

6.2.3 The arguments of the examining division concerning an improvement or synergistic effect (*supra*) are also not valid for these claims, as these claims do not require such an effect. Such an argument could be of relevance in the discussion of inventive step, but not of sufficiency of disclosure.

6.2.4 As regards D4.1, cited by the examining division as an example that one of the combinations falling within the limits of the claim (decitabine plus IFN-γ) did not have an effect, the board follows the appellant's arguments that, in fact, this document further supports the concept underlying the invention. D4.1 discloses (page 5222, last paragraph and page 5223, first paragraph) that cell lines which are non-responsive to decitabine do not show a high up-regulation of gene expression in the same genes which are up-regulated in cells that are responsive to decitabine. According to D4.1, the cutaneous melanoma cell lines that are non-responsive to decitabine do not present a high enough up-regulation of gene expression in comparison to the uveal melanoma cell lines. Re-expression of silenced genes is an outcome of the hypomethylating activity of decitabine, and D4.1 regards this difference in re-expression as the reason behind the sensitisation of uveal melanoma cell lines, but not of cutaneous melanoma cell lines, to IFN-γ by decitabine. Finally, D4.1 does demonstrate that decitabine and IFN-γ (and also IFN-α) had an effect on uveal melanoma cells.

6.3 Independent claim 36: Kits

6.3.1 Although claim 36 is directed to a "kit for treating a disease...", thus raising doubts whether it is directed to a product with no purpose restrictions, or whether it has the scope of a purpose-restricted product claim (see also below), the same considerations as discussed above apply also to this claim. Hence, for the reasons given above, this claim is also considered to fulfil the requirements of Article 83 EPC.

Remittal to the first instance

7. The examining division's decision was based only on Article 83 EPC (in conjunction with Rule 42(1)(e) EPC). Novelty and inventive step thus still have to examined and the board notes that a number of documents have been cited in the search report as X. Moreover, there is no indication on file that other EPC requirements such as Article 123(2) EPC or Article 84 EPC have yet been assessed. In particular, it has to be examined whether all new combinations of features and new dependencies of claims do have a basis in the application as filed. Also some issues of lack of clarity are readily apparent, for example as mentioned above concerning the wording of claim 36, which raises doubts as to the claim category; a similar lack of clarity is also present in claim 19.

8. Although there is no absolute right to have an issue decided upon by two instances, it is also not the function of the board to consider and decide upon issues which have not been examined at all by the department of first instance. The board thus decides to exercise its discretion under Article 111(1) EPC and

remit the case to the first instance for further prosecution.

## Order

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

1. The decision is set aside.

2. The case is remitted to the first instance for further prosecution.

The Registrar: The Chairman:

N. Maslin U. Oswald

Decision electronically authenticated