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Datasheet for the decision of 5 August 2008

Case Number: T 0745/07 - 3.3.08

Application Number: 01119325.7

Publication Number: 1160319

IPC: C12N 15/11

Language of the proceedings: EN

Title of invention:
Antisense-oligonucleotides for the treatment of immunosuppressive effects of transforming growth factor-beta (TGF-beta)

Applicant:
BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH

Headword:
TGF-β2 antisense oligonucleotides/BIOGNOSTIK

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

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main and auxiliary request - inventive step (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0745/07 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 5 August 2008

Appellant: BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK mbH
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 19 December 2006 refusing European application No. 01119325.7 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
C. Rennie-Smith

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division posted on 19 December 2006 by which European patent application No. 01 119 325.7 (published as EP 1 160 319) was refused under Article 97(1) EPC 1973. The present application is a divisional application of the earlier European application No. 94 916 170.7.

II. In the decision under appeal, the examining division found that the amendments introduced into claim 1 of the sets of claims according to each of the main request and the second auxiliary request offended against Article 123(2) EPC because the passage on page 11, lines 6 to 9 of the application as filed did not provide a clear and unambiguous disclosure of a link between TGF-ß2 and either or both specific activities mentioned there. With respect to the first auxiliary request, the examining division found that, having regard to a combination of document (1) with either document (4) or document (9), an inventive step within the meaning of Article 56 EPC could not be acknowledged for the subject-matter of claim 1.

III. Together with the statement of grounds of appeal, the appellant (applicant) re-filed, as its main request and auxiliary request, the sets of claims according to the main request and the second auxiliary request on which the examining division based its refusal. The previous first auxiliary request was not pursued further. In case that either the main request or the auxiliary request was found to be in accordance with Article 123(2) EPC, the appellant requested remittal of the case to the examining division for further

prosecution. As a subsidiary request, oral proceedings were requested.

IV. The appellant was summoned to oral proceedings. In a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached to the summons, the board provided observations on issues relating to Articles 123(2) and 84 EPC.

V. On 1 April 2008, the appellant filed two sets of claims that replaced the previous claims as its main request and auxiliary request.

VI. Claims 1 and 8 according to the **main request** read as follows:

"1. Use of Antisense-oligonucleotides or effective derivatives thereof hybridizing with an area of a gene coding for transforming growth factor-ß (TGF-ß) for the preparation of a medicament for inhibition of pathological angiogenesis in the treatment of tumors, said antisense oligonucleotide or effective derivative thereof hybridizes with an area of a gene coding for transforming growth factor-ß2.

8. An antisense oligonucleotide or effective derivatives therefore[***sic***] hybridizing with an area of a gene coding for transforming growth factor-ß (TGF-ß) for inhibiting pathological angiogenesis in the treatment of tumors, said oligonucleotide or derivative thereof hybridizes with an area of a gene coding for TGF-ß2."

Dependent claims 2 to 6 concerned particular embodiments of the use of claim 1, and independent claim 7 was directed to a pharmaceutical composition comprising an antisense nucleic acid according to SEQ ID NOs: 57-71, 73-75, 77, 78, 80-82, 84, 86-135.

VII. At the oral proceedings held on 7 May 2008 the appellant amended its auxiliary request by filing claims 1 to 5 that replaced the set of claims previous on file.

VIII. Amended claims 1 and 5 of the **auxiliary request** read as follows:

"1. Use of Antisense-oligonucleotides **or modifications thereof** hybridizing with an area of a gene coding for transforming growth factor-ß**2** (TGF-ß**2**) for the preparation of a medicament for inhibition of pathological angiogenesis in the treatment of tumors, **wherein the antisense oligonucleotide has a sequence selected from Seq. ID. No. 57-71, 73-75, 77, 78, 80-82, 84, 86-135**.

5. An antisense oligonucleotide or **modifications** there**of** hybridizing with an area of a gene coding for transforming growth factor-ß**2** (TGF-ß**2**) for inhibiting pathological angiogenesis in the treatment of tumors, **wherein the antisense oligonucleotide has a sequence selected from Seq. ID. No. 57-71, 73-75, 77, 78, 80-82, 84, 86-135**." (differences with claim 1 of the main request have been highlighted by the board)

Claims 2, 5 and 6 according to the main request were deleted in the auxiliary request and the remaining

claims were renumbered and the dependencies adapted accordingly. Moreover, in dependent claim 2 - which corresponds to claim 3 of the main request - the language "*the modification of* [the antisense oligonucleotide]" was introduced, and in independent claim 4 - which corresponded to claim 7 of the main request - the language "*nucleic acid according to*" was replaced by "*oligonucleotide having a sequence selected from*".

IX. After the discussion on the requests on file, in particular with respect to the issue of inventive step, the board decided to adjourn the oral proceedings until 5 August 2008 for the sole purpose of allowing the appellant to file evidence in support of its allegation that the subject-matter of the claims according to the auxiliary request involved an inventive step. The appellant was given until 11 July 2008 to file such evidence.

X. On 11 July 2008, the representative of the appellant filed via fax a two-page letter including following submissions:

"*The effect of these antisense oligonucleotides* [the antisense oligonucleotides specified in claim 1; note by the board] *was investigated with the Atlas Human Cancer Array of Clontech using RNA and cDNA, respectively, isolated from the glioma cell line A-172, which is producing TGF-ß2 in a high amount.*

Samples of A-172 were incubated with an antisense oligonucleotide selected from the group consisting of SEQ ID No. 57-71, 73-75, 77, 78, 80-82, 84, and 86-135.

Negative controls of A-172 were likewise incubated without addition of an antisense oligonucleotide. RNA was isolated from the negative control as well as from the samples incubated with an antisense oligonucleotide. The RNA was transferred to cDNA via PCR, the cDNA was labeled with ^{32}P and hybridized to the Atlas Array.

The incubation of A-172 with an antisense oligonucleotide SED IQ [sic] *No. 57-64, 66-71, 73, 74, 77, 78, 80-82, 84, 86-91, 93-112, or 114-135 led to a more than 10-fold decrease of the VEGF expression in comparison to the negative control and thus, to a significant inhibition of angiogenesis.*

The incubation of A-172 with an antisense oligonucleotide SED IQ [sic] *No. 65, 75, 92, or 113 still resulted in a 3-fold decrease of the VEGF expression, which is quite efficient in the inhibition of angiogenesis in a tumor such as glioma.*

In contrast thereto, SEQ ID No. 136 for example did not show any effect on the expression of VEGF and is therefore not at all suitable for the inhibition of angiogenesis in the treatment of tumors."

XI. In a communication sent to the appellant by fax on 29 July 2008, the board expressed the provisional opinion that:

"... the statements made in appellant's letter cannot be considered as evidence that supports an inventive step of the subject-matter according to the auxiliary request. Due to the scarce information provided on the conditions under which the experiments were conducted

and the absence of any verifiable data concerning the results obtained, appellant's statements appear to be mere allegations devoid of probative value.

In the absence of ***verifiable*** *experimental evidence showing that the technical effect on which the invention is said to rely is in fact achieved, the board is presently not inclined to acknowledge an inventive step.*"

XII. In response to the board's communication, the appellant filed on 31 July 2008 additional experimental data and explanations.

XIII. On 5 August 2008, the oral proceedings adjourned from 7 May 2008 were resumed and the evidence submitted by the appellant was discussed.

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

(1): P. Jachimczek et al., 1991, Proceedings of the Annual Meeting of the American Association for Cancer Research, vol. 32, page 248, Abstract 1474;

(2): U. Bogdahn et al., March 1993, Proceedings of the Annual Meeting of the American Association for Cancer Research, vol. 34, page 518, Abstract 3091;

(4): M. Maxwell et al., May 1992, J. Neurosurg., vol. 76, pages 799 to 804;

(9): S. Bodmer et al., 15 November, 1989, The Journal of Immunology, vol. 143, No. 10, pages 3222 to 3229.

XV. The submissions made by the appellant, as far as they are relevant to this decision, may be summarized as follows:

Main request

Article 123(2) EPC

A basis for the feature "***inhibiting pathological angiogenesis***" could be found on page 11, second paragraph of the application as filed.

Article 56 EPC

The angiogenic properties of TGF-ß2 were not mentioned in either document (1) or document (2). Thus, in view of this prior art the technical contribution of the invention was to be seen in the provision of a new and inventive medical use of TGF-ß2 antisense oligonucleotides for the treatment of tumors by inhibiting pathological angiogenesis.

Since in 1987 only TGF-ß1 was known, a person skilled in the art could recognise that the angiogenic properties of TGF-ß described in documents (4) and (9) by reference to previous prior art documents were those of TGF-ß1, and not of TGF-ß2 as stated in (4) and (9). Thus, the suggestions made in these documents would not have been taken into account by the skilled person

seeking to solve the objective technical problem solved by the present invention.

Auxiliary request - Article 56 EPC

The antisense oligonucleotides specified in claim 1 were able to inhibit pathological angiogenesis via reduction of the expression of the vascular endothelial growth factor (VEGF) which was involved in angiogenesis. Consequently, the claimed use involved an inventive step in view of documents (1) and (9) as none of these documents provided any hint to the strong inhibitory effect of the particular antisense oligonucleotides on angiogenesis in the treatment of tumors.

XVI. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request filed on 1 April 2008 or the auxiliary request filed during the oral proceedings on 7 May 2008.

Reasons for the Decision

Main request

Article 123(2) and 84 EPC

1. Claim 1 is drafted as a "Swiss-type" second medical use claim and differs from the corresponding claim of the main request on which the examining division decided, in that the medical indication is defined as "*for inhibition of pathological angiogenesis* ***in the treatment of tumours***", and that the term "*nucleic acid*"

has been replaced by "*antisense oligonucleotide or effective derivative thereof*".

2. The latter amendment was introduced to overcome an objection under Article 84 EPC raised in the board's communication under Article 15(1) RPBA (see Section III above). In the board's view, this amendment does not introduce subject-matter which extends beyond the content of the application as filed, and is thus allowable under Article 123(2) EPC.

3. As concerns the therapeutic indication specified in claim 1 ("*in the treatment of tumors*"), a basis is found in page 11, lines 6 to 9 of the application as filed, read in connection with claim 2 as originally filed. In this context it should be noted that the use of TGF-ß2 antisense oligonucleotides for the manufacture of a medicament **for treating tumors** represents the actual therapeutic indication disclosed in the passage of the application as filed which constitutes the basis for the present claim 1, the inhibition of pathological angiogenesis rather being one of two possible mechanisms disclosed in the application on which the medical use of TGF-ß2 antisense oligonucleotides for tumor treatment may rely.

4. With respect to these two mechanisms, it is worth noting that at the priority date of the application the immunosuppressive and angiogenic properties of TGF-ß2 were known in the art, as is particularly apparent from documents (4) and (9) cited on page 12, lines 13 to 16 and 6 to 8 of the application as filed.

5. In view of the above, the amended set of claims according to the main request is considered to fulfil the requirements of Article 123(2) EPC, as well as those of Article 84 EPC.

Novelty - Article 54 EPC

6. Since the issue of novelty was not dealt with in the decision under appeal, the board assumes that the examining division had no concerns in this respect. Nor does the board, as none of the documents presently on file discloses the specific medical use of TGF-ß2 antisense oligonucleotides claimed in claim 1.

Article 56 EPC - Inventive step

7. Claim 1 according to the main request is directed to the use of TGF-ß2 antisense oligonucleotides for the manufacture of a medicament for the treatment of tumours by inhibiting pathological angiogenesis.

8. TGF-ß2 (transforming growth factor-ß2) is a member of the TGF-ß family of multifunctional polypeptides that regulates cell growth and development, and is secreted by tumour cells. The TGF-ß2 protein has autocrine activity, i.e. is able to support the growth of the tumour cells that secrete it. An important role of TGF-ß2 in the development of human glioblastomas (malignant brain tumours) is suggested in documents (9) and (4) (see document (9), last sentence of the abstract on page 3222, and document (4), paragraph bridging the left and right hand columns on page 803).

9. For the assessment of inventive step following the "problem-solution" approach, either document (2) or document (1) may be taken as starting point.

10. Document (2), which is an abstract published in March 1993 included in the proceedings of the annual meeting of the American Association for Cancer Research, describes that the use of phosphorothioate antisense oligodeoxynucleotides targeted against TGF-ß2 led to a reduction up to 30% (compared to control nonsense oligodeoxynucleotides) of glioma cell proliferation ***in vitro***, whereas only 25% inhibition was obtained using neutralizing anti-TGF-ß2 antibody (see lines 5 to 10 of document (2)).

11. Similar observations are reported in the earlier document (1) published in 1991, which is also an abstract included in the proceedings of the annual meeting of the American Association for Cancer Research. This document describes a study in which target lymphocytes obtained from two glioblastoma early passage cell cultures were incubated with TGF-ß-phosphorothioate-antisense-oligonucleotides derived from a TGF-ß consensus sequence, ie a sequence having a motive which is common to different members of the TGF-ß family. Among the members of the TGF-ß family, TGF-ß2 is specifically mentioned at the beginning of the document and described as a suppressor of anti-tumor cytotoxic T-lymphocyte activation within malignant CNS-tumors ***in vivo*** and of cytotoxic attack of $CD8^+$ lymphocytes which proliferate upon stimulation with autologous tumor targets ***in vitro*** (see lines 1 to 4 of document (1)). The results of the preliminary experiments with TGF-ß antisense oligonucleotides

described in document (1) indicated an enhancement of lymphocyte proliferation up to 3-fold, and of autologous tumor cytotoxicity up to 50%. The authors of document (1) concluded that these observations may have implications for ***in vivo*** activation of $CD8^+$ lymphocytes within malignant gliomas.

12. Starting from either document (2) or document (1) as the closest prior art, the objective technical problem to be solved is to provide a therapeutic application for the TGF-ß2 antisense oligonucleotides described in these documents.

13. The solution proposed in claim 1 is the use of antisense oligonucleotides or effective derivatives thereof which hybridize with the gene encoding TGF-ß2 for manufacturing a medicament for treating tumours by inhibiting pathological angiogenesis.

14. The board considers that, in view of the fact that TGF-ß2 had been suggested repeatedly as a strong suppressor of the immune response to tumor cells, it was obvious to a person skilled in the art to consider using TGF-ß2 antisense oligonucleotides as described in documents (2) and (1) to block the synthesis and secretion of TGF-ß2 protein in tumor cells, with the aim of hindering the development of the tumor. In view of the results reported in documents (2) and (1) and in the absence of any evidence to the contrary, it is assumed that the skilled person had also a reasonable expectation that this approach would work.

15. The board is not convinced by appellant's arguments that neither document (2) nor document (1) mentioned

the angiogenic properties of TGF-ß2, and that no results were presented in these documents showing that the angiogenic activity of TGF-ß2 may be inhibited using antisense oligonucleotides.

16. First, it should be stressed again that the therapeutic indication specified in claim 1 is not the inhibition of angiogenesis as such, but the use the TGF-ß2 antisense oligonucleotides for treating tumors, the inhibition of angiogenesis being only a mechanism on which the treatment of tumors relies. Since the use of TGF-ß2 antisense oligonucleotides for treating tumors by inhibiting the suppressor activity of TGF-ß2 was obvious in view of document (2) or (1), the mere suggestion of a further mechanism on which this obvious use may rely does not support an inventive step within the meaning of Article 56 EPC, especially in view of the fact that the mechanism in question was already suggested in the prior art.

17. In fact, it was stated in prior art document (9) that "Provided its local secretion by glioblastoma cells, G-TsF/TGF-ß2 may contribute to impaired immunosurveillance of tumor development. [...] in addition to its effect on the immune system, G-TsF/TGF-ß2 may also enhance tumor (glioblastoma) cell proliferation in an autocrine way, a mechanism of neoplastic cell growth for which circumstantial evidence has accumulated. **Since TGF-ß has been shown to be angiogenic (44), the local secretion of G-TsF/TGF-ß2 by glioblastoma cells may contribute to proliferation of tumor endothelial cells which is a hallmark of high grade gliomas**." (see page 3228, left column, third paragraph; relevant passage highlighted by the board).

18. Similar conclusions are drawn also in prior art document (4) in view of the fact that TGF-ß2 mRNA and its protein product were found in high levels in glioblastoma, while absent from normal brain tissue. Having regard to the potent immunosuppressive and angiogenic properties of TGF-ß2, the authors held that TGF-ß2 overexpression may contribute to both the immunosuppression and neovascularisation characteristics of glioblastoma patients (see page 800, left column, last sentence of the first paragraph). See also the chapter under the heading "*Perivascular lymphocytic infiltrate*" and the conclusions on page 803.

19. It follows from the above that, at the relevant date of the present application, secretion of TGF-ß2 by tumor cells was considered to contribute to tumor development by inducing proliferation of tumor endothelial cells and neovascularization.

20. The appellant alleged that a person skilled in the art would have noticed that the scientific publications referred to in documents (9) and (4) in respect of the angiogenic activity of TGF-ß2 related rather to TGF-ß1 than to TGF-ß2 because at that time only TGF-ß1 was known. The board disagrees. It cannot be taken from the title of the references cited in documents (9) and (4) to which member of the TGF-ß family were attributed angiogenic properties. Thus, in the absence of a compelling reason to question the statements in documents (9) and (4), a person skilled in the art would have taken the statements at their face value, rather than checking whether or not they were scientifically sound.

21. Finally, the board notes that, while it is true that documents (2) and (1) do not provide any results showing that the angiogenic activity of TGF-ß2 can be inhibited by antisense oligonucleotides, neither does the present application. Moreover, no convincing experimental evidence has been submitted by the appellant during examination or on appeal.

22. For the reasons above, the board concludes that the subject-matter of claim 1 does not involve an inventive step. Thus, the main request cannot be granted.

Auxiliary request

23. Claim 1 is directed to the use of specific TGF-ß2 antisense oligonucleotides defined by their nucleotide sequence, for the manufacture of a medicament for treating tumors by inhibiting pathological angiogenesis (see Section VIII above).

24. The documents presently on file do not disclose or suggest any of the antisense oligonucleotides recited in the claim, nor their use in the treatment of tumors. Thus, having regard to the prior art on file, the claimed subject-matter would appear, in principle, not to be obvious to a person skilled in the art.

25. However, as none of the examples in the application as filed concerned any of the antisense oligonucleotides specified in claim 1, the question arises whether or not the specific antisense oligonucleotides recited in the claim solve the technical problem they purportedly

solve. The appellant bears the burden of proof in this respect.

26. Even though oral proceedings were adjourned in order to give the appellant the opportunity to prepare and submit experimental evidence showing that the technical effect on which the claimed use relies is in fact achieved, no such evidence was submitted. The submission of the representative of the appellant dated 11 July 2008 (see Section X above) contained scarcely any information on the conditions under which the alleged experiments had been conducted, and no verifiable data at all. A classical "paper example", at its best.

27. As the board indicated in its communication in preparation for the second oral proceedings, the statements made by the representative of the appellant concerning the effect of the antisense oligonucleotides on the expression of VEGF are only mere assertions and have no evidential value whatsoever.

28. As concerns the data submitted on 31 July, the board was not able to establish whether or not at least one of the tested oligonucleotides corresponded to any of the antisense oligonucleotides specified in claim 1. At the oral proceedings, the representative of the appellant admitted that this was not the case.

29. Thus, in the absence of evidence showing that the problem purportedly solved by the invention is in fact solved using the antisense oligonucleotides recited in claim 1, the requirement of inventive step is

considered not to be fulfilled. Therefore, the auxiliary request cannot be granted.

Remittal to the examining division

30. The appellant requested that the case be remitted to the examining division for further examination, in particular with respect to the requirement of inventive step.

31. Pursuant to Article 111 EPC, a board of appeal may either exercise any power within the competence of the department which was responsible for the decision under appeal, or remit the case to that department for further prosecution.

32. Since in the decision under appeal the examining division already identified the relevant prior art and expressed an adverse opinion on the issue of inventive step, and the amended claims filed on appeal did not introduce new aspects that justified a remittal, the board, in the interests of procedural economy and effectiveness, refused the appellant's request for remittal. The board, however, ensured that in the course of the appeal proceedings the appellant was given ample opportunity to file any arguments or evidence it wished to submit.

33. With regard to the findings above, the appeal, however, cannot be allowed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow L. Galligani