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Datasheet for the decision of 16 January 2015

Case Number: T 2200/11 - 3.3.08

Application Number: 03792075.8

Publication Number: 1532249

IPC: C12N15/11

Language of the proceedings: EN

Title of invention:
RNAI PROBES TARGETING CANCER-RELATED PROTEINS

Applicant:
THE UNIVERSITY OF BRITISH COLUMBIA

Headword:
Silencing interference dsRNA clusterin inhibition cancer Alzheimer/ BRITISH COLUMBIA

Relevant legal provisions:
EPC Art. 83, 84
EPC R. 139
RPBA Art. 12(4)

Keyword:
Main Request and new evidence - admissibility (no);
Auxiliary Request -
clarity (no); sufficiency of disclosure (no);

Decisions cited:
G 0003/89, G 0011/91, G 0010/93, T 0506/04, T 0699/06

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Catchword:

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Case Number: T 2200/11 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 16 January 2015

Appellant: (Applicant)	THE UNIVERSITY OF BRITISH COLUMBIA University-Industry Liaison Office, No. 103-6190 Agronomy Road Vancouver, British Columbia V6T 1Z3 (CA)
Representative:	Frei Patent Attorneys Frei Patentanwaltsbüro AG Postfach 1771 8032 Zürich (CH)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 18 April 2011 refusing European patent application No. 03792075.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	M. Wieser
Members:	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division to refuse the European patent application no. 03 792 075.8 (published as International patent application WO 2004/018676, hereinafter "*the application as filed*") pursuant to Article 97(2) EPC on the grounds of lack of inventive step (Article 56 EPC) and insufficiency of disclosure (Article 83 EPC).

II. Basis for the refusal were a Main Request and a first and second Auxiliary Request filed with a letter dated 8 October 2010.

The Main Request consisted of eight claims, with independent claims 1, 4, 6 and 7 reading as follows:

"1. An RNA molecule having a sequence effective to mediate degradation or block translation of mRNA encoding clusterin, characterized in that the RNA molecule consists of a sequence or a complementary pair of sequences selected from among Seq. ID Nos. 1 to 16, 61 and 62."

"4. A pharmaceutical composition comprising an RNA molecule according to any one of claims 1 to 3 and a pharmaceutically acceptable carrier."

"6. Use of an RNA molecule in accordance with any of claims 1 to 3 in formulating a pharmaceutical composition for the treatment of cancer or Alzheimer's disease."

"7. An RNA molecule in accordance with any one of claims 1 to 3 for the treatment of cancer or Alzheimer's disease."

Claims 2-3 and 5 were directed to preferred embodiments of claims 1 and 4, respectively. Claim 8 was directed to preferred embodiments of claims 6 or 7, defining a selection of specific forms of cancers.

Claim 1 of the First Auxiliary Request read as follows:

"1. An RNA molecule having a sequence effective to mediate degradation or block translation of mRNA encoding clusterin, characterized in that the RNA molecule consists a complementary pair of sequences selected from among Seq. ID Nos. 1 to 16."

Claim 1 of the Second Auxiliary Request read as follows:

"1. An RNA molecule having a sequence effective to mediate degradation or block translation of mRNA encoding clusterin, characterized in that the RNA molecule consists a complementary pair of sequences selected from among Seq. ID No. 5 and 6 or from Seq. ID No. 9 and 10."

Both Auxiliary Requests consisted of eight claims, wherein independent claims 4, 6 and 7 read as in the Main Request.

III. With reference to decision T 699/06 of 29 June 2010, the examining division stated that, where a therapeutic application was claimed in the form of either a composition for a specific therapeutic use or a use of a composition for the manufacture of a medicament for a

defined therapeutic application, attaining the claimed therapeutic effect was a functional feature of the claim. As a consequence thereof, under Article 83 EPC, unless this was already known to the skilled person at the priority date, the application had to disclose the suitability of the composition for the claimed therapeutic application. The examining division considered that this was not the case for the present application and thus, claims 6 and 7 were considered to lack sufficient disclosure (cf. page 10, point 2.8 of the decision under appeal).

IV. With the statement setting out the Grounds of Appeal, the appellant filed a new Main Request and an Auxiliary Request, replacing the previous requests on file, together with new documentary and experimental evidence (Applied Biosystems document and attachments A and B, respectively). The appellant further provided an amended copy of page 24 of the description of the application as filed and requested two corrections on this page under Rule 139 EPC.

Claim 1 of the **Main Request** read as follows:

"1. An RNA molecule having a sequence effective to mediate degradation or block translation of mRNA encoding clusterin, characterized in that the RNA molecule consists a complementary pair of sequences selected from among Seq. ID No. 1 and 2 or Seq. ID No. 5 and 6 or from Seq. ID No. 9 and 10 or Seq. ID No. 61 and 62."

Claims 2-5 were directed to preferred embodiments of claim 1. Except for the amendments in the claim dependencies, claims 6-10 read as claims 4-8 of the Main Request underlying the decision under appeal.

As regards the objection raised by the examining division under **Article 83 EPC**, the appellant referred to the experiments carried out in the Examples (and to Figures 1-5 and 8-10) of the application as filed which showed the technical effect in lowering clusterin gene expression in *in vitro* cell cultures. Moreover, reference was made to prior art documents, cited in the application as filed and in the decision under appeal (page 6, lines 5-21 of the application as filed and page 10, points 2.5-2.6 of the decision under appeal), which taught the suitability of lowering clusterin gene expression for the treatment of cancer and of Alzheimer disease. Therefore, according to the appellant, the claimed therapeutic effect, i.e. lowering clusterin gene expression, was disclosed in the prior art and the achievement of this effect by the claimed RNA molecules was documented in the application as filed. Thus, the requirements of Article 83 EPC were fulfilled.

V. The appellant was summoned to oral proceedings. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), the appellant was informed of the board's preliminary, non-binding opinion on the relevant issues of the case.

In particular, the board questioned the admissibility into the appeal proceedings of the new Main Request and the newly filed evidence. It was noted that the Auxiliary Request filed with the Grounds of Appeal was identical to the Second Auxiliary Request underlying the decision under appeal and thus, already formed part of the appeal proceedings.

Appellant's attention was drawn to the decision G 10/93 (OJ EPO 1995, page 172, Headnote), stating that, in an

appeal from a decision of an examining division, the board had the power to examine whether the application fulfilled all the requirements of the EPC. Accordingly thereto, the board raised several objections under Article 84 EPC, alone or in combination with Article 83 EPC, against the subject-matter claimed in both the Main Request and the Auxiliary Request (*infra*). As regards Article 56 EPC, the board made several observations concerning both the Main Request and the Auxiliary Request. In the light of the criteria set out in the decisions G 3/89 and G 11/91 (OJ EPO 1993, pages 117 and 125, respectively), observations were also made regarding the appellant's request for corrections on page 24 (legends to Figures 8 and 9).

In view of these considerations, the board informed the appellant of its intention to dismiss the appeal based on the written submissions and the evidence on file.

VI. The appellant informed the board of its intention not to attend the oral proceedings scheduled for the 27 November 2014 and withdrew its request for oral proceedings. No substantive reply to the objections raised by the board in its communication pursuant to Article 15(1) RPBA were provided by the appellant.

VII. The scheduled oral proceedings were cancelled.

VIII. The following documents are cited in this decision:

D1: WO 02/22635 (publication date: 21 March 2002);

D6: P. Strocchi et al., NeuroReport, 3 June 1999; Vol. 10, No. 8, pages 1789 to 1792;

D8: N-H. Choi-Miura and T. Oda, Neurobiology of Aging, 1996, Vol. 17, No. 5, pages 717 to 722;

D10: M. Calero et al., Microsc. Res. Tech., 2000, Vol. 50, pages 305 to 315;

D12: S.E. Jones and C. Jomary, Int. J. Biochem. Cell Biol., 2002, Vol. 34, pages 427 to 431;

D23: R. Agami, Current Opinion in Chemical Biology, 2002, Vol. 6, pages 829 to 834.

IX. The appellant (applicant) requested to set aside the decision under appeal and to grant a patent on the basis of the Main Request or, in the alternative, the Auxiliary Request filed with its statement of Grounds of Appeal. The appellant also requested to introduce two corrections on page 24 of the description of the application as filed (Rule 139 EPC).

Reasons for the Decision

1. In view of the fact that the appellant has not provided any substantive reply to the comments made and the objections raised by the board in its communication pursuant to Article 15(1) RPBA (cf. point VI *supra*), the present decision is essentially based on the board's preliminary view given in this communication.

Admissibility of the Main Request and of the new evidence

2. The Main Request is new in the proceedings and, as such, was never filed during the examination phase.

Although it is acknowledged that the subject-matter of the requests considered by the Examining Division comprised the complementary pair of sequences SEQ ID No. 1 and 2 (by use of the wording "*a complementary pair of sequences selected from among SEQ ID Nos. 1 to 16*"), the specific pair of complementary sequences SEQ ID NO: 1 and 2 was not specifically identified as such, not even in a dependent claim. No reasons have been provided by the appellant to explain why the Main Request has been introduced at this late stage of the proceedings and why it could not have been filed during the first instance proceedings (Article 12(4) RPBA).

The subject-matter of the Main Request suffers, *prima facie*, from the same deficiencies as former requests on file (*infra*) and its filing in appeal proceedings is not in line with the purpose of an appeal proceedings, which is to review a decision taken by the department of first instance and not to give the applicant the opportunity to reshape the claims and/or to introduce amendments arbitrarily (cf. "Case Law of the Boards of Appeal of the EPO", 7th edition 2013, IV.E.1 and IV.E. 4.4, pages 934 and 1003, respectively).

3. With regard to the late filed documentary and experimental evidence (see point IV *supra*), the board notes the following:

Already in its communication dated 2 December 2010 annexed to the summons to oral proceedings, the examining division explicitly referred to the relevance of the alleged technical effect for the assessment of inventive step of the claimed complementary pair of selected sequences, in particular, with regard to Auxiliary Request 2 in examination, for the specific sequences Clu3 and Clu5. The appellant, however,

instead of submitting further substantive arguments or amending the claims, withdrew its request for oral proceedings and did not make any substantial submission (cf. page 2, points 1.12 and 1.13 of the decision under appeal).

The board also notes that identical references to the relevance of the alleged technical effect were also explicitly present in previous communications of the examining division (cf. page 3, point 3.3 of the communication dated 22 June 2010 and page 2, point 3.2 of the communication dated 16 February 2010).

Thus, the experimental evidence (Attachments A and B) and the documentary evidence (Applied Biosystems document, "siRNA Design Guidelines") filed by the appellant with its statement setting out the Grounds of Appeal cannot be considered to be a direct reply to an issue raised for the first time in the decision under appeal. Rather, this evidence addresses an issue that was known to be of importance since an early stage of the proceedings. Thus, the evidence could and should have been filed earlier.

4. In view of the above considerations, the board decides not to admit the Main Request and the new evidence filed with appellant's statement setting out the Grounds of Appeal into the appeal proceedings (Article 12(4) RPBA).

Auxiliary Request

5. The Auxiliary Request filed with appellant's statement of Grounds of Appeal is identical to the Second Auxiliary Request underlying the decision under appeal, which was originally filed on 8 October 2010. Thus, the

Auxiliary Request is already part of the appeal proceedings.

6. In the decision under appeal the examining division considered only Articles 56 and 83 EPC. No comments were made with regard to the requirements of Articles 123(2), 84 and 54 EPC. No objections were ever raised under Articles 84 and 54 EPC by the examining division and, in the communication of 2 December 2010 annexed to the summons to oral proceedings, the examining division acknowledged all requests then on file to fulfil the requirements of Article 123(2) EPC.

7. According to decision G 10/93 (OJ EPO 1995, page 172, Headnote), in an appeal from a decision of an examining division, the board has the power to examine whether the application meets all the requirements of the EPC. In view of the claimed subject-matter and of the appellant's arguments in the statement of Grounds of Appeal, the board considers that it is necessary to assess whether the requirements of Article 84 EPC, alone or in combination with Article 83 EPC, are fulfilled.

Article 84 EPC

8. The "*RNA molecule*" according to claim 1 is defined as consisting of a complementary pair of sequences (cf. point II *supra*). However, these complementary sequences are not required to be in "*a duplex RNA form*", as required in dependent claims, or in "*a duplex siRNA*" or "*double-stranded RNA*", as mentioned in the description of the application as filed (cf. *inter alia*, page 15, line 13 and page 23, lines 5-6 from the bottom). The absence of such a requirement renders the subject-

matter of the claims ambiguous and open to interpretation.

The fact that the "*RNA molecule*" is also required in claim 4 to be comprised in "*a pharmaceutical composition*" raises additional questions, such as: Is claim 1 directed to a single product or does it comprise two different products? Does it include compositions in which the complementary sequences are not in a duplex form? Is the technical effect cited in the claim achieved by both sequences in a duplex form or only by the presence of the antisense RNA?

9. The claimed "*pharmaceutical composition*" is characterized by two components, namely "*an RNA molecule*" as defined in claim 1 (and claims dependent thereupon) and "*a pharmaceutically acceptable carrier*" (cf. point II *supra*), which is defined in a dependent claim merely as a "*sterile injectable solution*". Claim 6 is directed to the use of said "*RNA molecule*" in "*formulating a pharmaceutical composition*", wherein the composition is not further defined (cf. point II *supra*).

The application as filed discloses the dilution of duplex RNA in a commercial serum free medium and a suitable reagent for transfection of cell cultures (cf. page 16, lines 4 to 6 and page 17, lines 3 to 9). It is questionable whether such a commercial product is "*acceptable*" for the treatment of human cancer or Alzheimer's disease. The different requirements that have to be fulfilled by a transfection of a cell culture and the treatment of cancer or Alzheimer's disease in a human body are extremely important and do not allow a simple extrapolation of systems and products used in one or the other. The board notes that

the "*pharmaceutical composition*" does not contain a simple RNA molecule but "*a duplex RNA*" which must not be altered or destroyed by other components present in the composition, such as the "*acceptable carrier*". This requirement further highlights the importance of satisfying rather exacting conditions for the treatment of these diseases.

Moreover, the "*pharmaceutical composition*" must also have a composition that allows an effective, efficient and specific delivery of the duplex RNA to the treatment site within the human body. There is no disclosure in the application as filed of a "*pharmaceutical composition*" or components thereof that allow a skilled person to maintain the RNA molecule in "*a duplex RNA form*" and, at the same time, to have the required effectivity, efficiency and specificity of delivery to the target cancer cells in a human body.

It is doubted that this deficiency can be overcome by reference to the common general knowledge of a skilled person working in the field of RNA interference or to general prior art in this field concerning antisense RNA inhibition. The nature and properties of antisense RNA (modified so as to be stable, specific and effective) are not directly comparable to those of a duplex RNA molecule (cf. *inter alia*, document D1 and decision T 506/04 of 5 December 2006). It is also questionable whether a mere extrapolation of systems and products used in antisense RNA technology is possible for siRNA and/or duplex RNA molecules. In any case, such information is not present in the application as filed (Article 83 EPC, *infra*).

10. Whereas in the application as filed reference is always made to "*sarcomas <u>such as</u> osteosarcoma*" (underlining by

the board; cf. page 1, line 31 and page 6, line 15), claim 8 of the Auxiliary Request refers to "*sarcomas, osteosarcoma*", implying that the latter is not a subgroup of the former.

Article 83 EPC

11. According to the appellant, claims directed to the therapeutic use of the claimed duplex RNAs or to their use in the formulation of pharmaceutical compositions for these therapeutic uses are based on the effects shown to be obtained in the application as filed for *in vitro* cultures of cancer cells (cf. point IV *supra*).

12. The *in vitro* effects referred to by the appellant are shown in the application as filed for the duplex RNA molecules of SEQ ID NO. 1 (58) and 2 (59) (CLU1, CI-I), SEQ ID NO. 5 (64) and 6 (65) (CLU3, CI-III), SEQ ID NO. 9 (67) and 10 (68) (CLU5, CI-IV) and SEQ ID NO. 61 and 62 (CI-II). However, as correctly noted by the examining division (cf. page 10, point 2.8 of the decision under appeal), according to the case law of the Boards of Appeal, "*the application must disclose the suitability of the substance or composition for the claimed therapeutic application*" (cf. T 699/06, *supra*, point 19 of the Reasons). The board considers these *in vitro* results to be necessary but not sufficient to demonstrate that these duplex RNA molecules are "*suitable*" for the claimed *in vivo* therapeutic applications. The following issues cast doubts on this suitability and are relevant for the board to arrive at a decision under Article 83 EPC:

12.1 In Example 2 of the application as filed, it is stated that "*BLAST analysis showed no homology with other known human genes*" (cf. page 16, lines 23 to 24 of the

application as filed). However, it is known that transfected siRNAs may regulate numerous transcripts which have a limited, low or partial, homology to the duplex RNA. This "*off-target transcript silencing*" is widespread and limits the specificity of the siRNA by hindering its use for therapeutic purposes (presence of significant undesired side effects). The undesired silencing effect cannot be eliminated by sequence selection and requires (sequence-independent chemical) modifications and optimization of the duplex RNA. However, there is no information in the application as filed that would allow a skilled person to overcome these undesired side effects.

It is also noted that, according to Example 2 of the application as filed, CI-III (SEQ ID NO. 5/64 and 6/65, CLU3) is located in a region 1620 nts downstream of the clusterin gene transcription codon (within the 3' UTR region of this gene; see "*Target site*" 1620 on page 84, Table 1 of document D1) and that CI-IV (SEQ ID NO. 9/67 and 10/68, CLU5) is located at the (human) clusterin transcription initiation site (see "*Target site*" 44 on page 83, Table 1 of document D1). Transcription initiation sites and 3'UTR regions usually have a significant degree of homology among different genes. Thus, it has to be expected that off-target transcript silencing may be present and relevant for these (unmodified, non-optimized) duplex RNA molecules.

12.2 In this context, it is noted that the *in vitro* experiments reported in the application as filed are concerned, only and exclusively, with mRNA and protein levels of human clusterin. There is no information about the level of cellular mRNA or proteins in general, or on a control of these levels in untreated cancer cells. The application does not provide any

information on the possible degree of homology of the complementary pair of both sequences of the claimed duplex RNA molecules to other sequences present in the human genome, on the presence or absence of partial homology to other human genomic sequences, let alone information on the effect of the claimed duplex RNA molecules on the mRNA and protein levels of these possible homologous human genomic sequences present in the cancer cells used in the *in vitro* experiments.

Moreover, most of the experiments reported in the application as filed rely on cell number counting (apart from measuring levels of clusterin mRNA transcript) which might well be influenced by the cell-adhesion properties of the clusterin protein. There is no experimental evidence in the application as filed showing the (increase/decrease) effect of the claimed duplex RNA molecules on other relevant transcripts involved in cancer, such as on p53 and/or bcl-2 proteins (cf. page 8, lines 7 to 9 of the application as filed).

12.3 As indicated in point 9 *supra*, the disclosure of the application as filed has to be sufficient for a skilled person to deliver the claimed duplex RNA molecules efficiently, effectively and specifically - maintaining them in a duplex form - to the target cancer cells in a human body. The board cannot see that a skilled person, at the priority date of the application, was in a position to obtain suitable formulations and systems to deliver, efficiently, effectively and specifically, duplex RNA molecules to the human body in general and to each of the various cancer types cited in the claims of the Auxiliary Request (prostate, sarcomas, etc.) as well as to cells involved in Alzheimer's disease (cf. *inter alia*, page 833, left-hand column of document

D23). The application as filed refers only "*to reach plasma and tissue concentrations suitable for the regulation of the targeted mRNA and protein*" without providing any further information (cf. page 15, lines 4 to 10 of the application as filed).

12.4 It is known in the art that siRNA duplexes are potent activators of the mammalian immune system. After administration in mammals, depending on the delivery system used and the specific siRNA sequence and/or structure, they can induce high levels of inflammatory cytokines and type I interferons resulting in a severe and acute toxicity that prevents their safe and efficient use in therapeutic applications. The presence of, *inter alia*, multiple uridine residues in close proximity is necessary for mediating such immune response. Whereas SEQ ID NO 1/58, SEQ ID NO 5/64 and SEQ ID NO 10/68 have only one subsequence of two contiguous uridine residues, SEQ ID NO 6/65 has two subsequences of two contiguous uridine residues and one subsequence of four contiguous uridine residues. The effect of these sequences on the induction of a human immune response is not known and no information is provided by the application as filed.

12.5 In the light of the prior art on file, the role of the clusterin protein in Alzheimer's disease was not well-established at the priority date of the present application. Whereas, on the one hand, clusterin inhibits Aß aggregation and is thus neuroprotective according to the aggregation toxicity hypothesis, on the other hand, clusterin enhances the oxidative stress of Aß exacerbating possible neuronal damage (cf. documents D6, D8 and D10). As acknowledged in document D12, clusterin seems to have a dual role, a normal protective function and a damaging effect, depending on

the cellular context and the molecular species (and their level) present in said context. The role of clusterin in Alzheimer's disease is also further complicated by the presence of several forms of clusterin having different cellular locations (sCLU and nCLU) (cf. page 21, lines 1 to 9 of the application as filed). In the absence of reliable information on clusterin's role, which is not disclosed in the application as filed, a therapeutic use of the claimed duplex RNA molecules in Alzheimer's disease is only highly speculative and not based on scientific or technical facts. Such a use may achieve, at least under certain conditions, results completely contrary to those desired.

Conclusion regarding Articles 84 and 83 EPC

13. In view of the fact that the appellant failed to address the objections raised by the board in its communication pursuant to Article 15(1) RPBA (cf. point 1 *supra*), the board sees no reason to deviate from its preliminary opinion set out in this communication. Thus, the appellant's Auxiliary Request does not fulfil the requirements of Articles 84 and 83 EPC.

Further substantive issues and appellant's requests

14. In the light of the above decision with regard to the requirements of Articles 84 and 83 EPC, there is no need for the board to consider and further elaborate on other pending objections, such as those under Article 56 EPC. There is also no need for the board to consider appellant's request for correction of page 24 of the description of the application as filed (Rule 139 EPC; cf. points IV and IX *supra*).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated