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D E C I S I O N
of 14 September 2005

Case Number: W 0041/04 - 3.3.04

Application Number: PCT/GB 03/04798

Publication Number: WO-04/042083

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Nucleic acid ligands and uses therefor

Applicant:
University of Leeds

Opponent:
-

Headword:
Nucleic acid ligands/UNIVERSITY OF LEEDS

Relevant legal provisions:
PCT Art. 17(3)(a)
PCT R. 13.1, 13.2, 40.1, 40.2

Keyword:
"Unity of invention (yes)"
"Additional search fee - refund - (yes)"

Decisions cited:
G 0002/89, W 0016/00

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: W 0041/04 - 3.3.04

International Application No. PCT/GB 03/04798

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 14 September 2005

Applicant: University of Leeds
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Representative: Couchman, J.
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Decision under appeal: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 16 July 2004.**

Composition of the Board:

Chair: U. Kinkeldey
Members: M. Wieser
B. Günzel

Summary of Facts and Submissions

I. International patent application No. PCT/GB 03/04798 having the title "Nucleic acid ligands and uses therefor" was filed with thirty-four claims.

Claim 1 read:

"A purified and isolated non-naturally occurring nucleic acid ligand to a fibrillar protein target, wherein said ligand is an RNA ligand selected from the group comprising:

(i) the nucleic acid depicted in any of SEQ ID NOS: 1-55 or 58-105;

(ii) having the corresponding DNA or RNA sequences of any one of SEQ ID NOS: 1-55 or 58-105 or the corresponding fully complementary sequences thereof or their L-ribose derivatives;

(iii) derivatives of the sequences depicted in any one of SEQ ID NOS: 1-55 or 58-105 having at least about 60%, 70%, 80% or 90% sequence identity to any one of the nucleotide sequences, and which have a binding affinity to a fibrillar protein."

Dependent claims 2 to 13 referred to preferred embodiments of the nucleic acid ligand, claim 14 related to a vector and claim 15 to a host containing at least one of said ligands. Claims 16 to 18 referred to a binding motif retaining the ability of a protein to form amyloid fibrils. Claim 19 was directed to a ligand to a cross β-core protein. Claims 20 to 28

related to pharmaceutical preparations and their use in therapeutic and diagnostic methods containing the claimed nucleic acid ligands. Claims 29 to 34 referred to a method for isolating the nucleic acid ligands and the products obtained.

II. The European Patent Office (EPO), acting in its capacity as International Searching Authority (ISA) under Article 16 PCT and 154 EPC, informed the Applicants that the application did not comply with the requirement of unity of invention (Rule 13.1 PCT) and invited the Applicants to pay fees for 105 additional inventions, i.e. a sum of 99.225 Euros in accordance with Article 17(3)(a) PCT and Rule 40.1 PCT.

The 106 inventions defined by the ISA were characterized as follows:

III. "Invention I (claims 1-6, 12-15, 20-34, all partially)

A purified and isolated non-naturally occurring RNA ligand (labelled or unlabelled) to A-Beta-40 monomeric target protein consisting of the nucleic acid sequence with SEQ ID NO: 1, a vector comprising said RNA ligand, a host cell comprising said vector, a pharmaceutical composition comprising said RNA ligand, the use of said RNA ligand for manufacture of a medicament, and a method for the isolation of said RNA ligand."

Inventions 2 to 103 were defined essentially as invention I above, but limited to the respective SEQ ID NOS: 2 to 55 and 58 to 105 and to the respective target proteins. Inventions 104 to 106 were defined to refer to peptide sequences consisting of SEQ ID NOS: 111, 112

and 113 respectively as a target for RNA aptamers, which sequences retain the ability of a protein to form amyloid fibrils.

IV. The common concept which could link inventions 1 to 106, as required by Rule 13.1 PCT, was seen in the provision of nucleic acid ligands (RNA aptamers) to fibrillar protein targets and target sequences therefore. This link was not considered to be a single inventive concept in the sense of Rule 13.2 PCT because it was known from the disclosure in the following documents, which disclosed RNA aptamers specific for amyloid proteins Beta-A4(1-40) and Beta-A4(1-42):

(D1) Biochemical and Biophysical Research Communication, vol.290, 2002, pages 1583 to 1588;

(D2) DE-A-199 16 417

The technical problem to be solved by the present application in the light of the disclosure in (D1) and (D2) was regarded as the provision of alternative RNA aptamers and targets.

The ISA stated that nucleic acid ligands had been designed for any target molecule ((D1) abstract). As these ligands could be routinely applied for any form of fibrillar protein of interest, the additional feature that the claimed aptamers bound to alternative forms of a fibrillar protein (e.g. monomeric, pre-fibrillar, proto-fibrillar, mature or immature) could not be considered to have an inventive character. As no other technical feature linked the different RNA aptamers claimed, each of them represented a separate

solution to the underlying technical problem. As the application, moreover, did not allow to group together any of the claimed RNA aptamer sequences with the target sequences of inventions 104 to 106, the claims related to 106 different inventions.

V. The Applicants paid one additional search fee for a search of invention 61 under protest (Rule 40.2(c) PCT). The protest fee was paid at the same time.

In the reasoned statement of the letter of protest they argued, as a main request, that the aptamers claimed were linked as follows:

"(i) they are directed to a class of proteins which, though diverse, all share the same common secondary structure (the cross β-core structure);

(ii) they bind to the cross β-core structure;

(iii) they unpredictably block fibril formation."

Secondarily, as auxiliary measure, the Applicants protested that the amount of the required additional fees was excessive. They filed in this respect four auxiliary requests. In the first three of these requests they suggested that the aptamers of claim 1 could be related to two, respectively three, respectively four different inventions. According to the fourth auxiliary request they asked that the Board of its own motion finds an alternative less harsh formulation than the ISA.

VI. The protest was reviewed in accordance with Rule 40.2(e) PCT by a review panel of the ISA. It held that the invitation to pay the additional search fees was justified. The review panel stated inter alia that feature (i), as defined by the Applicants (see section (V) above) was unable to be a special technical feature making a technical contribution over the prior art (Rule 13.2 PCT), as document (D1) disclosed aptamers against Beta-A4(1-40), i.e. one of the same class of proteins as described in claim 1. Also feature (ii) identified by the Applicants, namely the capability of the claimed aptamers to bind to the beta-core structure, could not be used as unifying linking concept. This was not a feature of claim 1, which required in point (iii) only that the claimed derivatives of SEQ ID NOS 1-55 and 56-105 should have binding affinity to a fibrillar protein. With regard to feature (iii) identified by the Applicants as unifying concept linking the aptamers of claim 1, namely their ability to block fibril formation, the ISA found that this property had been specified in the present application in relation with two aptamers only, SEQ ID NO 38 and SEQ ID NO 74, thus not for the aptamers of inventions 1 and 61. The ISA concluded that

"[c]onsidering said property is apparently so surprising, it would appear to require that more than two of the many aptamers of the present application should be tested in this respect to verify that this may be considered a general property."

The ISA decided that the inventions relating to SEQ ID NOS 38 and 74 were searched at no additional costs.

VII. In a response to the review panel's communication the Applicants argued as follows:

Document (D1) disclosed aptamers to aggregated amyloid proteins which were unable to bind to monomeric amyloids. The remarkable and unexpected property of two representative examples of the claimed nucleic acid ligands, SEQ ID NO 38 and SEQ ID NO 74, to block fibril formation, could be extrapolated to all aptamers represented by SEQ ID NOS 1-55 and 58-105. According to an alternative argument (defined as *"Protest Auxiliary Request"*) the Applicants stated that the unifying concept of the present application was the ability of the aptamers of claim 1 to be useful in monitoring the progression of an amyloid disease, contrary to the aptamers of document (D1) directed to mature plaque aggregates which are present at the final stage of a disease only.

Reasons for the Decision

1. The protest complies with the requirements of Rule 40.2(c) and (e) PCT and is therefore admissible. The Applicants' submissions in the reasoned statement and as quoted in section (V) above imply that the Applicants request to have the additional search fee reimbursed.

2. Under Article 154(3) EPC the Boards of Appeal rule on protests against additional fees charged by the ISA under Article 17(3) (a) PCT. Under Rule 40.2(c) PCT they examine the protest and, to the extent that they

find it justified, order the total or partial reimbursement of the fees.

It follows from these provisions that the Board is not competent to deal with the Applicants' auxiliary requests submitted in the reasoned statement of their letter of protest (see section (v) above), wherein they requested the Board to group the inventions differently as this was done by the ISA in their invitation to pay additional search fees, or to find *"of its own motion ... an alternative less harsh formulation".* The only question that can be decided by the Board is whether or not there is a common inventive concept linking inventions 1 and 61 and consequently whether or not the additional search fee for invention 61, paid under protest, will be reimbursed.

3. The international application was considered to lack unity of invention on an "a posteriori basis", i.e. after an assessment of the claims with regard to novelty and/or inventive step in relation to the prior art. In the case of an "a posteriori" lack of unity it should be examined after it has been shown that there is a lack of novelty or inventive step in a main claim (in the present case, in one embodiment of the main claim) whether there is a technical relationship among the remaining inventions involving one or more of the same or corresponding special technical features (see G 2/89, OJ EPO, 1991, 166, points (4) and (5) of the reasons; PCT Search Guidelines as in force from 18 September 1998, Chapter VII, item 9; Rule 13.2 PCT; W 16/00 dated 20 September 2000, point (3) of the reasons). The ISA relied on the prior art documents (D1) and (D2).

4. According to the invitation of the ISA, the common technical feature between the various embodiments of claim 1 was seen in the provision of nucleic acid ligands (RNA aptamers) to fibrillar protein targets. However, this feature was known from (D1) and (D2) which disclosed RNA aptamers specific for fibrillar amyloid protein Beta-A4(1-40) and Beta-A4(1-42). The ISA further considered that the common problem linking the 103 different nucleic acid ligands of claim 1 (SEQ ID NOS 1-55 and 58-103) was the provision of alternative RNA aptamers to those of (D1) and (D2). In the absence of any other special technical feature it was concluded that each one of the different RNA aptamers of claim 1 represented a separate solution to this common problem.

5. In the reasoned statement of their letter of protest the Applicants argued that all aptamers of claim 1 not only bound to fibrillar proteins but also blocked fibril formation. They referred to example 6 which showed that an aptamer corresponding to SEQ ID NO 74 definitely had this ability, which could be extrapolated to all of SEQ Id NOS 1-55 and 58-103.

Following this line of argumentation the problem to be solved by the present application should be seen in the provision of nucleic acid ligands (RNA aptamers) specific for amyloid proteins **and** being able to block fibril formation.

6. The PCT Guidelines state in Chapter 10.01 that the determination if the inventions in an international application are so linked as to form a single general

inventive concept is "made on the contents of the claims as interpreted in the light of the description and drawings (if any)".

Thus, according to these Guidelines, the evaluation of the issue of unity of invention on the basis of what is derivable from the disclosure of the application is a correct approach justifying an invitation to pay additional fees if unity of invention cannot be acknowledged on the basis of such evaluation.

7. In the present case the international application in various passages refers to the role of aptamer reagents in the inhibition of fibrillogenesis.

The Board considers in this respect especially figure 1 and the corresponding legend on page 15, lines 15 to 20 to be important. Figure 1 shows models for how aptamer reagents might inhibit fibrillogenesis, either by stabilising the monomeric form (top line, right hand side of figure 1) or by directly blocking fibril growth (lower line of figure 1).

In examples 4 (SEQ ID NO 38) and 6 (SEQ ID NO 74) it is shown and explicitly stated that two examples of the aptamers of claim 1 reduce fibril formation in an in vitro fibrillation assay (see page 28, lines 7 to 11, and lines 27 to 30; also page 21, lines 4 to 17, page 16, lines 8 to 18, page 17, lines 1 to 5 and figures 5B, 6 and 10).

On page 7, lines 11 to 14, it is stated that the isolated aptamers according to the present application have been discovered to have properties that make them

potentially useful entities, in contrast to the aptamers disclosed in reference document (14). This reference corresponds to present document (D1).

8. Document (D1) does not mention or suggest a potential role of the aptamers disclosed therein in the inhibition of fibrillogenesis. Document (D2), on page 3, lines 64 to 66 reads:

"Der Einsatz als Mittel zur Behandlung kann beispielsweise eine Modifikation der Aptamere derart umfassen, dass β-Amyloide komplexiert werden und so die Plaquebildung verhindert wird oder bereits gebildete Plaques abgebaut werden."

This statement in the final paragraph of the description of (D2) is not substantiated by an example and does not disclose or suggest that aptamers (without modification) can block fibril formation.

9. The ISA decided that the aptamers of claim 1 are not linked by the special technical feature that they are able to block fibril formation based on the argument that this ability has been explicitly shown for two out of 103 claimed sequences only, not including SEQ ID NOS 1 and 61. Point (5) of section (4.2.c) of the review panel's communication reads:

"Therefore, the ability of aptamers of invention 61 and 1 to inhibit fibril formation is mere speculation...Considering said property is apparently so surprising, it would appear to require that more than two of the many aptamers of the present

application should be tested in this respect to verify that this may be considered a general property."

Thus, their finding that the feature of blocking fibril formation is not a special new and inventive feature as required by Rule 13.2 PCT, and their decision arrived at in consequence, namely lack of unity of invention, contrary to the requirements of Rule 13.1 PCT, is based on the assumption that the results of specific examples 4 and 6 cannot be extrapolated to the other aptamers of claim 1.

This assumption is not substantiated by providing verifiable technical facts and/or a reference to the prior art and is in contradiction to the assertions made by the Applicants.

10. The Enlarged Board of Appeal in decision G 2/89 (supra; point (8.2) of the reasons) holds that the consideration by an ISA of the requirement of unity of invention should, of course, always be made with a view to giving the Applicant fair treatment and that the charging of additional fees under Article 17(3)(a) PCT should be made only in clear cases. In particular, in view of the fact that such consideration under the PCT is being made without the Applicant having had an opportunity to comment, the ISA should exercise restraint in the assessment of novelty and inventive step and in border-line cases preferably refrain from considering an application as not complying with the requirement of unity of invention on the ground of lack of novelty or inventive step.

10.1 The ability of nucleic acid ligands (RNA aptamers), which are specific for amyloid proteins, to block fibril formation is not disclosed in documents (D1) and (D2). The Board notes that also the review panel, saying that it is mere speculation that the aptamers of inventions 1 and 61 have this ability, does not argue that this feature is known from the prior art documents on file (cf point (4.2.c) of the review panel's communication).

10.2 In the light of the disclosure in documents (D1) and (D2), as discussed in point (8) above, the Board in the present case concludes that it is not a **clear case,** as defined by the Enlarged Board of Appeal, that the ability of blocking fibril formation is an obvious feature of RNA aptamers specific for amyloid proteins.

11. Consequently, the Board disagrees to the ISA's finding that there is no common technical feature susceptible of linking the subject matter of inventions 1 and 61 together, which is based on an assumption only (see point (9) above).

12. Therefore, the Board cannot follow the ISA's reasoning, according to which the searched subject-matter (inventions 1 and 61) is considered as not complying with the requirement of unity of invention.

Order

For these reasons it is decided that:

1. Refund of the one additional search fee paid by the Applicants is ordered.

2. The protest fee shall be refunded.

Registrar: Chair:

P. Cremona U. Kinkeldey