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Datasheet for the decision of 2 April 2019

Case Number: T 2232/13 - 3.3.08

Application Number: 10007677.7

Publication Number: 2239329

IPC: C12N15/113

Language of the proceedings: EN

Title of invention:
Therapeutic compositions

Applicant:
Alnylam Pharmaceuticals, Inc.

Headword:
iRNA duplex/ALNYLAM PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 54, 76, 123(2)

Keyword:
All requests - added matter - (yes)
Main request - novelty (no)

Decisions cited:

Catchword:

Europäisches Patentamt
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Office européen des brevets

Beschwerdekammern

Boards of Appeal

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Case Number: T 2232/13 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 2 April 2019

Appellant: (Applicant)	Alnylam Pharmaceuticals, Inc. 790 Memorial Drive Cambridge MA 02139 (US)
Representative:	Lenhard, Konstanze Müller-Boré & Partner Patentanwälte PartG mbB Friedenheimer Brücke 21 80639 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 15 May 2013 refusing European patent application No. 10007677.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	D. Pilat
	J. Geschwind

Summary of Facts and Submissions

I. The appeal lies from a decision of an examining division posted on 15 May 2013, refusing the European patent application N°10 007 677.7 under Article 97(2) EPC. The application with the title "Therapeutic compositions" is a divisional application, in accordance with Article 76 EPC, of the earlier European patent application N° 04 718 537.6 (published as International patent application WO 2004/080406).

II. In the decision under appeal, the examining division held that claims 1, 8 and 10 to 12 of the main request lacked novelty over document D1 (Article 54(1)(2) EPC). The examining division also found that amended claim 1 of the auxiliary requests 1 and 2 lacked novelty over document D1.

III. Together with its statement setting out the grounds of appeal, the appellant filed four sets of amended claims as its main request and first to third auxiliary requests.

IV. The appellant was summoned to oral proceedings. In a communication sent in preparation of the oral proceedings, the board expressed its provisional opinion inter alia on the compliance of the new requests with the requirements of Articles 123(2) and Article 54 EPC.

V. Oral proceedings were held on 2 April 2019.

VI. Claim 1 of the main request reads as follows:

"1. An iRNA duplex agent comprising a first and a second sequence, having at a selected or constrained

sequence, a first monomer in the first sequence, and a second monomer in the second sequence,
wherein the monomers are selected such that a first level of stability in the iRNA duplex agent between the first and second sequence, and a second level of stability in a duplex between the first or second sequence and a target sequence results, wherein the constrained or selected site is within three positions from the 3' end of the sense strand, wherein the iRNA duplex agent is represented by

S 5′ $R_1N_1N_2N_3N_4N_5$ [N] $N_{-5}N_{-4}N_{-3}N_{-2}N_{-1}R_2$ 3′
AS 3′ $R_3N_1N_2N_3N_4N_5$ [N] $N_{-5}N_{-4}N_{-3}N_{-2}N_{-1}R_4$ 5'

S:AS $P_1P_2P_3P_4P_5$ [N] $P_{-5}P_{-4}P_{-3}P_{-2}P_{-1}$ 5'

wherein
S indicates the sense strand; AS indicates antisense strand; R_1 indicates an optional 5′ sense strand overhang; R_2 indicates an optional 3' sense overhang; R_3 indicates an optional 3′ antisense sense overhang; R_4 indicates an optional 5′ antisense overhang; N indicates subunits; [N] indicates that additional subunit pairs may be present; and P_1 to P_5 and P_{-5} to P_{-1} indicates a paring of sense N_1 to N_5 and N_{-5} to N_{-1}, and antisense N_1 to N_5 and N_{-5} to N_{-1}, respectively, and wherein the iRNA is 21 to 23 nucleotides in length."

Dependent claims 2-12 are directed to particular variants of the product of claim 1.

VII. Claims 1 to 12 according to the main request differ from the claims underlying the decision under appeal in that claim 1 of the main request was amended to specify that

- the constrained or selected site is within three positions "from the 3' end of the sense strand" ... (emphasis added by the board).

VIII. Claims 1 to 12 according to the first auxiliary request differ from the claims of the main request in that claim 1 was further amended to specify that

- "the constrained or selected site contains a monomer substitution in the antisense strand which forms a mismatch with the target sequence," ... (emphasis added by the board).

IX. Claims 1 to 12 according to the second auxiliary request differ from the claims of the first auxiliary request in that claim 1 was further amended to specify that

- "the sense strand contains a monomer substitution which forms a canonical Watson Crick pairing with the substituted monomer in the antisense strand," ... (emphasis added by the board).

X. Claims 1 to 3 according to the third auxiliary request differ from the claims of the first auxiliary request in that claim 1 was further amended to specify that

- "the constrained or selected site contains a monomer substitution in the antisense strand which forms a mismatch with the target sequence, wherein the pair P_{-1} is A:U or U:U"(emphasis added by the board).

XI. The following document is referred to in the present decision:

D1: M. AMARZGUIOUI et al., "Tolerance for mutations and chemical modifications in a siRNA", Nucleic Acids Research, 15 January 2003, vol. 31, no. 2, pages 589-595.

XII. The submissions made by the appellant concerning issues relevant to this decision, were essentially as follows:

Article 123(2) EPC - Added matter

The amended set of claims 1 to 12 of the main request derived from the main request underlying the decision under appeal. The amendment of claim 1 was inter alia supported by the content of the patent application on page 21, lines 17 to 19.

The amended set of claims 1 to 12 of the first auxiliary request derived from the main request underlying the decision under appeal. The amendments were inter alia supported by the content of the patent application on page 21, lines 17 to 19 and page 59, lines 11 to 19.

The amended set of claims 1 to 12 of the second auxiliary request derived from the main request underlying the decision under appeal. The amendments were inter alia supported by the content of the patent application on page 2, lines 28 to 29, page 20 lines 17 to 28, page 21 lines 17 to 19 and page 59, lines 11 to 19.

The amended set of claims 1 to 3 of the third auxiliary request derived from the first auxiliary request underlying the decision under appeal. The amendments were inter alia supported by the content of the patent

application on page 21, lines 17 to 19 and page 59, lines 11 to 19.

None of the amended claims of the main and auxiliary requests 1 to 3 filed with the appeal introduced subject matter beyond the content of the patent application.

Article 54 EPC - Novelty

The subject matter of claims 1 to 12 of the main request and of the first to third auxiliary requests was novel in view of document D1.

Document D1 did not disclose any iRNA agents that have a base pair within three positions from the 3' end of the sense strand that results in different levels of stability when the level of stability of the iRNA duplex agent is compared to one of the strands of the duplex agent with its target sequence.

All iRNA agents described in document D1 were fully complementary to the target sequence at the 5’ end of the antisense strand.
Since the degree of complementarity between the antisense sequence of an iRNA agent with its target sequence was highly relevant, the nucleic acid sequences of both strands of the iRNA duplex were imposed by the target sequence when designed to target a particular target sequence. The nucleic acid sequence of the sense strand of an iRNA duplex depended on the nucleic acid sequence of the antisense strand, which was itself specified by the nucleic acid sequence of the target sequence. Hence, if the level of stability between one strand of an iRNA duplex and its target sequence was altered, this altered stability could only

be introduced by modifying one strand of the iRNA duplex, while altering the level of stability between both strands of an iRNA agent could be achieved by modifying either the sense or antisense strand of said iRNA duplex. A different level of stability between strands of an iRNA duplex and one strand of the iRNA duplex and its target sequence could only be obtained when at least one strand of the iRNA duplex was modified compared to a regular iRNA duplex.

Even if document D1 had an A:U base pair within three positions from the 3' end of the sense strand, it did not anticipate the claimed subject matter of the third auxiliary request because these pairs did not cause any mismatch of the antisense strand with the target sequence. The adenosine base in the sense strand corresponded to an adenosine base in the target sequence at the same position.

XIII. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of its main request or any of the first to third auxiliary requests.

Reasons for the Decision

1. The duly summoned appellant did not attend the oral proceedings, which in accordance with Rule 115(2) EPC and Article 15(3) RPBA took place in its absence.

Article 113 (1) EPC

2. The board, in its communication pursuant to Article 15(1) RPBA, expressed a reasoned provisional opinion on the issues to be discussed at the oral proceedings which included inter alia the issues of admission of

the sets of amended claims filed in appeal proceedings and their compliance with the requirements of the EPC.

3. In reply to the board's communication, the appellant did not submit any substantive arguments in relation to the issues raised therein. Moreover, by not attending the oral proceedings, the appellant decided not to avail itself of another opportunity to orally address or comment on the issues raised by the board in its communication for defending its case.

4. According to Article 15(3) RPBA, the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying on its written case. The present decision is therefore based on the same grounds, arguments and evidence on which the provisional opinion of the board was based.

Main Request and first to third auxiliary requests.
Admission into the appeal proceedings

5. The amended claims of the main request and the first to third auxiliary requests, submitted with the statement of grounds of appeal, constitute an attempt to remedy the deficiencies reported in the decision under appeal and put forward during oral proceedings before the opposition division. The board, decides to admit them into the appeal proceedings.

Main request

Article 123 (2) EPC and 76 EPC

The description and the figures of the divisional patent application and the parent application are literally identical. Thus, when assessing whether there is a direct and unambiguous disclosure of the claimed subject matter in the patent application and its parent application, reference is only made to the description of the International patent application WO 2004/080406.

6. Amended claim 1 relates to an iRNA duplex agent ... wherein the constrained or selected site is within three positions from the 3' end of the sense strand, ...

7. Basis for this amendment was indicated to be found inter alia on page 21, lines 17 to 19, of the description which reads:

> "*A constrained or selected site can be present at a number of positions in the iRNA agent duplex. E.g., a constrained or selected site can be present within 3, 4, 5, or 6 positions from either end, 3'or 5'of a duplexed sequence.*"

The selected site can also be present in the middle of the duplex region, as stated in the sentence immediately following the recited sentence.

8. The board considers that the definition of the iRNA duplex of claim 1, containing a constrained or selected site selected to be within 3 positions, out of a list of 3, 4, 5, or 6 positions, selected to be at an 3' end, out of the 3' or 5' ends or the middle of the

duplex region, and ultimately selected to be located on the sense strand out of both strands of the duplex, results from a combination of three specifically selected options whose combination is not directly and unambiguously, neither explicitly nor implicitly, derivable from the patent application, for example from page 21, lines 17-19 of the patent application. Thus, the subject matter of claim 1 of the main request contravenes Articles 76(1) and 123(2) EPC.

Claim interpretation

9. For assessing the novelty of claim 1, it is crucial to determine which monomers compose the sequences of the iRNA duplex. They are defined by means of a first and second level of stability, both dependent on a target sequence.

According to page 19, line 22 to page 20, line 7, of the patent application, the "level of stability" means the level of stability in a duplex, either between the two separate molecules (strands) of a double stranded iRNA agent or between a sequence (strand) of an iRNA agent and another sequence molecule, "e.g. a target or off-target sequence in a subject". The pairing between monomers of a first sequence molecule with a second sequence molecule in the iRNA agent duplex results in a first level of stability, while the pairing of a first sequence molecule (strand) of an iRNA duplex with another sequence molecule (target or off-target sequence) results in a second level of stability. In case a duplex between an antisense sequence of an iRNA agent and a target mRNA has a greater level of stability compared to the level of stability measured for the complementary sequences of said iRNA agent duplex, the sequences of the iRNA duplex have a lower

free energy of dissociation and a lower Tm compared to the free energy of dissociation observed between the sequence of the iRNA agent and its target sequence (see page 21, lines 9-13). The reversed level of stability for both sequence pairs reported above is equally envisaged (see page 20, lines 8-16).

The board notes that the "target sequence" in claim 1 is only characterized by name. It may be any nucleotide sequence of interest to the skilled person. It follows that any alteration of the degree of complementarity between the target sequence and the antisense strand of the iRNA duplex can be the result of either an alteration of the antisense strand of the iRNA duplex or of a mismatched position in the strand sequence of the target sequence. Thus, the level of stability between two fully complementary strands of the iRNA duplex will differ from the level of stability between one strand of the iRNA duplex and a non-fully complementary target sequence (e.g. single-nucleotide polymorphic mutant). This difference in stability is inevitable.

Novelty (Article 54(2) EPC)

10. Document D1 discloses the effects of mutations and chemical modifications at various positions in siRNA agents targeting the human Tissue factor (htf) mRNA. It discloses multiple siRNA agents of 21 nucleotides in length having A:U base pairs at their 5' antisense ends and multiple G:C base pairs at their 5' sense ends. Some siRNA agents have 2' sugar modified monomers: 2'-*O*-Methyl or 2'-*O*-Allyl modifications at their end (D1, Figure 3). The chemically modified versions of the siRNA hTF167i M1+1, M0+2, M2+2 and M2+4 in Figure 3, all have a length of 21 nucleotides and have a 2'-*O*-

methylated adenosine or/and 2'-*O*-methylated uridine located within three positions from the 3' end of the sense strand. The selected site incorporates a 2'-*O*-methylated adenosine and/or a 2'-*O*-methylated uridine in the sense strand or/and antisense strand of the iRNA duplex agent. The target sequence corresponds to positions 167-187 in hTF having the wild type sequence:

5'- cggcgcuucaggcacuacaaaua-3'
3'- gccgcgaaguccgugauguuuau-5'

11. Since "a target sequence" according to claim 1 is in no way structurally limited, any nucleic acid sequence, for instance a sequence derived from the hTF target sequence, may be regarded as a suitable target sequence.

For instance the following sequences, derived from positions 167 to 187 of hTF, having at least one nucleotide mutation at positions 185 to 187 may be regarded as target sequences according to claim 1:

5'- cggcgcuucaggcacuacaa**UAU**-3'
3'- gccgcgaaguccgugauguu**AUA**-5'

5'- cggcgcuucaggcacuacaa**GCG**-3'
3'- gccgcgaaguccgugauguu**CGC**-5'

5'- cggcgcuucaggcacuacaa**CGC**-3'
3'- gccgcgaaguccgugauguu**GCG**-5'

5'- cggcgcuucaggcacuacaa**U**UA-3'
3'- gccgcgaaguccgugauguu**A**AU-5'

5'- cggcgcuucaggcacuacaa**C**UA-3'

3'- gccgcgaaguccgugauguu**G**AU-5'

The level of stability of the siRNA duplexes disclosed in Figure 3 of document D1, being fully complementary, and the level of stability of any one of the derived target sequences shown above, pairing with one of the non-fully complementary sense or antisense strands of the siRNAs, for example of the siRNAs labelled M1+1, M0+2, M2+2 and M2+4, must differ.

11.1 Thus, the siRNAs M1+1, M0+2, M2+2 and M2+4 disclosed in Figure 3 of document D1 fall within the scope of claim 1 of the main request.

12. The siRNAs M1+1, M0+2, M2+2 and M2+4 disclosed in Figure 3 of document D1 anticipate for the same reasons the subject-matter of

- claim 8 which requires at least one or more pairs in P_{-5} to P_{-1} to be A:U;
- claim 10 which requires at least one or more pairs in P_5 to P_1 be chosen from G:C A:T and A:U;
- claim 11 which requires at least 2 of the pairs in P_1 through P_4 be chosen from G:C;
- claim 12 which requires at least one or more pairs in P_{-5} through P_{-1} be chosen independently from the group of A:U, ..., and at least one or more pairs in P_5 to P_1 be chosen independently from the group of G:C, A:T, A:U, ... and a pair in which one or both subunits has a sugar modification,... .

First Auxiliary request (claims 1-12)

Amended claim 1, compared to claim 1 of the main request, further specifies that "... the constrained or selected site contains a monomer substitution in the

antisense strand which forms a mismatch with the target sequence, ...".

Article 123 (2) EPC and 76 EPC

13. As a basis for this amendment, the appellant referred inter alia to page 21, lines 17 to 19 and page 59, lines 11 to 19, of the description.

14. The description on page 59, lines 11 to 19, defines structures or functions, such as the complementarity of the iRNA agent. Although this passage discloses that a perfect complementarity is often desired, particularly in the antisense strand (with respect to the target RNA), some embodiments may include one or more, "preferably 6, 5, 4, 3, 2 or fewer mismatches (with respect to the target DNA", and if present, are preferably located "in a terminal region or regions, e.g. within 6, 5, 4, or 3 nucleotides of the 5' and/or 3' terminus".

15. The board considers that there is no basis in the recited passages of the patent application for an amended iRNA duplex as defined in claim 1, combining three arbitrarily selected features out of the lists of features disclosed on page 21, lines 17 to 19, of the description to define a constrained site (cf. point 8, *supra*), with the additional feature "... that the constrained or selected site in the antisense strand contains a monomer substitution in the antisense strand which forms a mismatch with the target sequence ", i.e. within three positions from the 3' end of the sense strand. Thus, in the absence of any direct and unambiguous disclosure derivable from the patent application for the specific combination of features characterizing the iRNA of amended claim 1, the board

concludes that the specific selection cannot, for the person skilled in the art, emerge directly and unambiguously from the content of the application as filed. Thus, the subject-matter of claim 1 contravenes Articles 76(1) and 123(2) EPC.

Second auxiliary request (claims 1-12)

16. Compared to claim 1 of the first auxiliary request, claim 1 of this request further specifies that " the sense strand contains a monomer substitution which forms a canonical Watson Crick pairing with the substituted monomer in the antisense strand, ...".

Article 123 (2) EPC and 76 EPC

17. As a basis for amended claim 1, the appellant referred inter alia to page 21, lines 17 to 19, page 2, lines 28 and 29, page 20, lines 17 to 28, and page 59, lines 11 to 19, of the description.

18. The patent application on page 2, lines 28-29, discloses that the first and second sequences of the iRNA agent are fully complementary. On page 20 of the patent application, it is explained that an intra-iRNA agent duplex has a first level of stability, and a second level for a duplex formed between a sequence of the iRNA and the target sequence, and that this can be obtained by selecting judiciously one or more monomers at a selected position, by selecting the position in the duplex to place the selected or constrained position and by selecting the sequence of the target sequence. The iRNA agent sequences satisfying these requirements are sometimes referred to as constrained sequences (see patent application page 20, lines 17 to 28).

19. As stated above, the board considers that there is no direct and unambiguous disclosure of the subject matter of claim 1 of the first auxiliary request. Consequently, there is also no basis in the recited passages for the definition of the claimed subject matter by yet a further feature, namely that the sense strand contain a monomer substitution which forms a canonical Watson Crick pairing with the substituted monomer in the antisense strand. Thus, the subject matter of claim 1 contravenes Articles 76(1) and 123(2) EPC.

Third auxiliary request (claims 1-3)

20. Compared to the first auxiliary request, claim 1 has been further amended to specify that the pair P_{-1} is A:U or U:U.

Article 123 (2) EPC and 76 EPC

21. As a basis for the amendments, the appellant referred to page 21, lines 17 to 19 and page 59, lines 11 to 19 and to page 152, lines 3 to 18 of the description.

22. The recited passage on page 152 of the patent application relates to subunit pairings and the preferred use of pairings decreasing the propensity to form a duplex at one or more of the positions in the duplex at the 5' end of the antisense strand. The modification at position P_{-1} is particularly preferred, alone or with modification(s) at other position(s), while it is preferred to select at least 1 of the pairs independently from the group of A:U; G:U; I:C or mismatched pairs.

23. Since the patent application does not directly and unambiguously disclose the iRNA duplex agent of claim 1 of the first auxiliary request, there is no basis for the subject matter of claim 1 of the third auxiliary request, defined by yet a further feature, either.

24. Since none of the requests on file meets the requirements of the EPC, the appeal must be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated