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Datasheet for the decision of 24 March 2021

Case Number: T 0752/17 - 3.3.08

Application Number: 05853546.9

Publication Number: 1819365

IPC: C12N15/11, C07H21/04, A61K31/7088

Language of the proceedings: EN

Title of invention:
Compositions and methods for inducing an immune response in a mammal and methods of avoiding an immune response to oligonucleotide agents such as short interfering RNAs

Patent Proprietors:
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Hornung, Veit
Endres, Stefan

Opponent:
CABINET MALEMONT

Headword:
Immunotherapy/ALNYLAM

Relevant legal provisions:
EPC Art. 54, 56, 87, 100(a), 100(b), 100(c)
RPBA Art. 12(4)

Keyword:
Added matter - (no)
Sufficiency of disclosure - (yes)
Priority - (yes)
Admission of new evidence - (no)
Novelty - (yes)
Inventive step - (yes)

Decisions cited:
G 0003/14, T 0292/85, T 0019/90, T 0024/91, T 0241/95, T 0158/96, T 0636/97, T 1045/98, T 1001/01, T 1811/13, T 1959/15

Catchword:

Europäisches Patentamt
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Case Number: T 0752/17 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 24 March 2021

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 1 March 2017 rejecting the opposition filed against European patent No. 1819365 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman B. Stolz
Members: M. R. Vega Laso
D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 819 365 with the title "Compositions and methods for inducing an immune response in a mammal and methods of avoiding an immune response to oligonucleotide agents such as short interfering RNAs" was granted from the European application No. 05853546.9 which was filed under the Patent Cooperation Treaty (PCT) claiming the priority of the earlier application US 634849 filed on 9 December 2004 ("the priority application"). In this decision, references to the "the application as filed" are to the PCT application published as WO 2006/063252.

II. The independent claims of the patent as granted read as follows:

"1. An isolated oligonucleotide agent for use in a method of immunotherapy by inducing or stimulating an immune response consisting of, or comprising a sequence, said sequence differing by not more than 2 nucleotides from SEQ ID NO: 1 provided that 4, 5, 6, 7 or 8 or more contiguous nucleotides are taken from the 5' end of SEQ ID NO: 1.

2. An in vitro method of stimulating an immune response in a cell comprising the step of administering to said cell an oligonucleotide agent according to claim 1.

10. A method of making an oligonucleotide agent so as to avoid stimulating an immune response in a mammal comprising the step of eliminating from a potential agent pool any agent that comprises a sequence, said sequence differing by not more than 2 nucleotides from SEQ ID NO: 1 provided that 4, 5, 6, 7 or 8 or more

contiguous nucleotides are taken from the 5' end of SEQ ID NO: 1.

11. A method of making an oligonucleotide agent so as to induce an immune response in a mammal, comprising the step of adding to a potential agent pool any agent that comprises a sequence, said sequence differing by not more than 2 nucleotides from SEQ ID NO: 1 provided that 4, 5, 6, 7 or 8 or more contiguous nucleotides are taken from the 5' end of SEQ ID NO: 1.

14. An iRNA agent comprising a sequence, said sequence differing by not more than 2 nucleotides from SEQ ID NO:1 provided that 4, 5, 6, 7 or 8 or more contiguous nucleotides are taken from the 5' end of SEQ ID NO: 1, for use in a method of immunotherapy by inhibiting the expression of a gene and inducing an immune response in a mammal.

16. A pharmaceutical composition comprising an oligonucleotide of any one of claims 1 or 3 to 8 and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is a vaccine.

17. A method of making an oligonucleotide agent so as to avoid stimulating an immune response in a mammal wherein said oligonucleotide comprises a sequence, said sequence differing by not more than 2 nucleotides from SEQ ID NO: 1 provided that 4, 5, 6, 7 or 8 or more contiguous nucleotides are taken from the 5' end of SEQ ID NO: 1, comprising providing the oligonucleotide agent in such manner that it contains at least 2, or at least 4, 2'-O-methyl modified nucleotides."

Dependent claims 3 to 9 and 19 relate to the oligonucleotide agent of claim 1 or the method of

claim 2. Dependent claims 12 and 13 are directed to variants of the method of claim 11. Dependent claims 15 and 18 relate to, respectively, an embodiment of the iRNA agent of claim 14 and a variant of the method of claim 17.

III. The patent was opposed on the grounds for opposition of Article 100(a) in conjunction with Articles 54 and 56; 100(b) and 100(c) EPC.

IV. In a decision posted on 1 March 2017, an opposition division found that none of the grounds for opposition prejudiced the maintenance of the patent as granted. Hence, the opposition was rejected.

V. The opponent (appellant) filed an appeal against the decision and submitted a statement setting out the grounds of appeal.

VI. The patent proprietors (respondents) replied to the statement of grounds of appeal and maintained their requests in opposition proceedings.

VII. The parties were summoned to oral proceedings before the board.

VIII. Both the appellant and the respondents made further submissions in preparation of the oral proceedings. However, by letter dated 24 February 2021 the appellant withdrew its request for oral proceedings and requested a decision in writing.

IX. In a communication sent in preparation of the oral proceedings, the board drew attention to matters which seemed to be of special significance and expressed a

provisional opinion on some of the issues raised by the appellant.

X. Oral proceedings were held on 24 March 2021 in the absence of the appellant.

XI. The following documents are referred to in this decision:

(8): V. Hornung *et al.*, March 2005, Nature Medicine, Vol. 11, No. 3, pages 263 to 270;

(9): S. S. Diebold *et al.*, 5 March 2004, Science, Vol. 303, pages 1529 to 1531;

(10): F. Heil *et al.*, 5 March 2004, Science, Vol. 303, pages 1526 to 1529;

(11): WO 03/086280 A2, published on 23 October 2003;

(16): Immunotherapy definition; http://dictionary.reference.com/browse/immunotherapy (accessed: November 05, 2015);

(17): J. M. B. Kaneene *et al.*, November 1978, Infection and Immunity, Vol. 22, No. 2, pages 486 to 491;

(18): A.-K. Yi *et al.*, 15 May 1998, The Journal of Immunology, Vol. 160, No. 10, pages 4755 to 4761;

(19): WO 2004/045543, published on 3 June 2004; and

(19a): Excerpt from the sequence listing of D19, SEQ ID NOs:3528540 and 3529550 to 3529600.

XII. The submissions made by the appellant relevant to the present decision were essentially as follows:

Article 100(c) EPC

The subject-matter of independent claims 1 and 14 extended beyond the content of the application as filed. There was no basis in the application for a method of immunotherapy by inducing or stimulating an immune response. The term "enhancing" disclosed on page 12, lines 23 to 25 of the application as filed could not serve as a basis for the broader wording "inducing or stimulating", and the combination of that feature with the feature "method of immunotherapy" was not supported by the original disclosure.

The application as filed did not disclose an *in vitro* method of stimulating an immune response. Plasmocytoid dendritic cells (PD cells) and HEK cells were used in the examples to test the potential of ssRNA molecules to induce the production of IFN-α; however, stimulation of an immune response was observed only in PD cells. Hence, not even the examples provided a basis for the subject-matter of claim 2.

Article 100(b) EPC

The claimed oligonucleotide agents were not enabled because the therapeutic effect recited in claim 1, namely to induce or stimulate an immune response, could not be plausibly achieved over the whole scope of the claim. The opposition division erred in finding that the feature "*for use in a method of immunotherapy by inducing or stimulating an immune response*" would functionally restrict the scope of claim 1 to immunostimulatory oligonucleotides. Claim 1 did not

specify a disease or pathological condition to be treated and thus could not be regarded as a second medical use claim under Article 54(5) EPC. If at all, the feature limited the scope of the claim to oligonucleotides suitable for use in a method of immunotherapy.

The term "oligonucleotide" was broad and included not only naturally occurring nucleotides, but also modified nucleotides as well as hybrid and chimeric oligonucleotides. Only some modified oligonucleotides exhibited stimulatory effects at all. As shown in the examples of the patent, LNA modifications at the 3' end strongly interfered with the activity of the oligonucleotide, and the 2'-O-methyl modification almost completely abolished the stimulatory activity. Moreover, even though the term "oligonucleotide" included also DNA oligonucleotides, only RNA oligonucleotides were exemplified in the patent. Document (11) provided evidence that the DNA counterparts of immunostimulatory RNA molecules might not have immunostimulatory activity.

Since claim 1 did not specify any number of nucleotide residues, the claimed oligonucleotides could consist of only seven nucleotide residues or up to 500. It was not plausible that the technical effect recited in claim 1 could be achieved by using nucleic acids of any length. As shown in the patent, oligonucleotides of 19 to 21 nucleotides in length induced the production of IFN-α in PD cells, but the induction achieved by shorter oligonucleotides having 12 or 16 nucleotides was drastically reduced compared to the 19mer oligonucleotides. Extrapolating the decrease in activity to shorter oligonucleotides, it was not

plausible that a 7mer oligonucleotide could have immunostimulatory activity.

Taking into account the enormous amount of oligonucleotides falling under the structural definitions in claim 1 and the complete absence of any guidance in the patent, a skilled person could not identify without undue burden those oligonucleotides potentially having immunostimulatory capacity, not only in terms of IFN-α production *in vitro*, but also being capable to induce or stimulate an actual immune response in a method of immunotherapy in a patient. Hence, the functional feature in claim 1 involved a full research programme in itself, rather than an enabling teaching.

In the example section of the opposed patent, only PD cells were shown to produce IFN-α in response to some of the tested RNA oligonucleotides. Without any further guidance as to which type of cell may be used to induce the desired immunostimulatory effect, the skilled person could not reproduce the method of claim 2 over its whole scope. Contrary to the opposition division's view, the lack of specification of the cell type was not a matter of willingness to understand, but a substantial lack of information in the opposed patent.

Article 100(a) EPC

Priority (Article 87 EPC)

The priority of the earlier US application could not be validly claimed. The specific combination of the two features "*consists or comprises a sequence which differs by no more than 2 nucleotides from SEQ ID NO:1*"

and "*4, 5, 6, 7, or 8 or more contiguous nucleotides are taken from the 5' end of SEQ ID NO:1*" in claim 1 of the patent could not be derived directly and unambiguously from the priority application. There was no hint of any kind in the priority application linking the two distinct embodiments disclosed in claim 3 and the passage on page 5, lines 3 to 9. The skilled person would not have considered combining those two embodiments because, from a technical point of view, it was not even possible to reconcile them. Contrary to the opposition division's view, the overall teaching could not support such a specific combination either.

It could not be derived from the disclosure on page 35 of the priority application that the first four nucleotides of SEQ ID NO:1 should be maintained. While that passage disclosed systematic base exchanges at the 3' end of SEQ ID NO:1, it was totally silent with respect to the number of base exchanges in general, i.e. at any position, as disclosed in claim 3 of the priority application. The question of whether the oligonucleotides defined in claim 1 of the patent were a "sub-class" of the oligonucleotides of claim 3 of the priority application, had no relevance at all for the validity of the priority.

Novelty (Article 54 EPC)

Since the priority could not be validly claimed, document (8) formed part of the state of the art under Article 54 EPC and deprived the claimed subject-matter of novelty. Also document (19) destroyed the novelty of the subject-matter of at least claims 1, 3, 4, 5, 6, 7 and 14.

Inventive step (Article 56 EPC)

Starting from either document (8) or document (9) as the closest state of the art, the claimed subject-matter did not involve an inventive step. The objective technical problem in view of document (9) was not solved, because there was no technical effect associated with the difference in only one nucleotide at the 5' end of SEQ ID NO:1 compared to the "RNA oligo 1" taught in document (9). In view of the teachings in document (10) or document (11), the subject-matter of claims 1 to 9, 14 to 16 and 19 was obvious to a person skilled in the art. Moreover, the method of independent claim 11 lacked an inventive step in view of document (11) as the closest state of the art, in combination with either document (9) or document (10). Dependent claims 12 and 13 were not inventive over document (11) in combination with document (9) and/or document (10).

XIII. The submissions made by the respondents were essentially as follows:

Article 100(c) EPC

The claimed subject-matter did not extend beyond the content of the application as filed. The disclosure at

page 5, lines 18 to 20 established a clear link between the agents of the invention and immunotherapy. The statement in that passage was not limited to a requirement of enhancing the immune response. Rather, the active agents were described as being immunostimulatory. As apparent from document (16), the term "immunotherapy" extended to both inducing and enhancing an immune response. The passage on page 15, second full paragraph of the application as filed provided a clear and unambiguous disclosure of *in vitro* applications, notably in a cell.

Article 100(b) EPC

No serious doubts, substantiated by verifiable facts had been raised that the invention could be carried out by a person skilled in the art over the whole scope of the claims. According to the settled case law of the Boards of Appeal, compliance with Article 83 EPC did not require that each and every embodiment falling under a claim was reduced to practice. Breadth of a claim was not *per se* a deficiency under Article 83 EPC.

The patent exemplified a number of ways to carry out the claimed invention and there was no evidence of failure. A line had to be drawn between lower immunostimulatory activity and no activity. Only certain and very specific modifications of the oligonucleotides resulted in reduced immunostimulatory activity. The patent itself provided a skilled person with a clear teaching of those few specific modifications which could be deleterious, and instructions as to where locked nucleotides could be placed within the molecule without interfering significantly with activity in cases where use of this particular type of modification was intended. Moreover,

the patent provided guidance for the skilled person as to which lengths were to be selected if particularly high immunostimulatory activity was desirable. It was apparent from document (11) that very short RNA molecules in a range between 5 and 40 nucleotides could have immunostimulatory activity. No research program would have been necessary to find out which oligonucleotides were functional.

The fact that transfection of oligonucleotide agents according to the invention failed to induce an interferon response in HEK 293 cells was not prejudicial to sufficiency of disclosure. When carrying out the method of claim 2, the skilled person would not use a cell line which, as known from the patent, was not capable of raising an immune response.

It was a well-established principle of the case law that *in vitro* data were a means to establish sufficient disclosure of second medical use claims (see decision T 1001/01 of 11 October 2007, section 3.2; and decision T 1045/98 of 22 October 2001, section 8).

Article 100(a) EPC

Priority (Article 87 EPC)

The relevant disclosure in the priority application was found in claim 3; and on page 5, lines 3 to 9; and page 35, lines 15 to 24. The claims by their very nature defined the invention, and the description added further features which the oligonucleotide agents of the invention may exhibit. There was no technical incompatibility between the two structural features of the oligonucleotides disclosed in the priority application.

Admission of documents (19) and (19a) into the proceedings (Article 12(4) RPBA)

Documents (19) and (19a) should not be admitted into the proceedings. While it had been cited in examination proceedings, document (19) did not automatically form part of opposition proceedings. Its content was less relevant than that of other documents on file, and its filing in appeal proceedings was belated.

Novelty (Article 54 EPC)

The content of document (8) did not form part of the art at the priority date.

Inventive step (Article 56 EPC)

A case of obviousness based on document (9) as the closest state of the art was bound to fail. Figure 3E of that document described two oligonucleotides, RNA oligo 1 and RNA oligo 2. The oligo 1 comprised a nucleotide sequence representing positions 2 to 6 of SEQ ID NO:1 of the patent in suit, but it was only oligo 2 which induced a strong interferon response. Hence, document (9) taught away from using oligo 1. Moreover, there was no suggestion in document (9) as to which sub-sequence within the sequence of oligo 1 would be responsible for the alleged interferon response. This was possible only by hindsight.

While documents (10) and (11) described sequences containing GU motifs as being immunostimulatory, the claimed invention did not seek to maximize GU contents. Rather, it was based on a different finding: the specific motif of SEQ ID NO:1 which provided a strong

stimulation of the immune system. There was no pointer or incentive for the skilled person to develop the teaching of those documents in the direction of the claimed invention.

The allegation that the technical problem had not been solved across the entire breadth of the claims had not been substantiated in terms of any particular subject-matter. The examples of the patent contained evidence, both *in vivo* and *in vitro*, of immunostimulatory activity of a plurality of oligonucleotides falling under the terms of the claims, and there was no requirement under the EPC to reduce each and every embodiment falling under the claims to practice.

XIV. The appellant requested in writing that the decision under appeal be set aside and that the patent be revoked. It also requested that documents (19) and (19a) be admitted into the proceedings.

XV. The respondents requested that the appeal be dismissed or, alternatively, that the decision under appeal be set aside and the patent maintained upon the basis of the auxiliary request filed under cover of a letter dated 25 November 2015. The respondents requested further that documents (19) and (19a) not be admitted into the proceedings.

Reasons for the Decision

Main request (patent as granted)

Article 100(c) EPC

1. In the decision under appeal, the opposition division considered that an isolated oligonucleotide agent having the structural features specified in claim 1 has a basis on page 6, lines 8 to 16 and page 13, lines 1 to 9 of the application as filed, and that the passage on page 1, lines 10 to 13 provides a link between immunotherapy and sequence specific oligoribonucleotide agents capable of **inducing** an immune response. In the opposition division's view, the passages on page 5, lines 18 to 20, and page 12, lines 20 to 23 provided a direct and unambiguous disclosure of single- or double-stranded oligonucleotides as **immunostimulatory** agents and their use for immunotherapy applications.

2. As regards claim 2, the passage on page 15, lines 11 to 16 of the application as filed was considered to indicate that an immunostimulatory agent can also act *in vitro* by stimulating certain responses in cells, and thus provide "*... the link between* ***immunostimulation*** *and* ***in vitro*** *cells*" (see last paragraph on page 9 of the decision under appeal). The same reasons given for claims 1 and 2 were said to apply to further claims which are dependent from or refer to claim 1 and/or 2.

3. In its statement of grounds of appeal, the appellant did not address the reasons given in the decision for the adverse findings on the objections under Article 100(c) EPC, but merely repeated *verbatim* the arguments presented in the notice of opposition. Those arguments did not persuade the opposition division that the claimed subject-matter extends beyond the content of the application as filed, and they fail also to persuade the board in appeal proceedings.

4. Contrary to appellant's view, the question of whether the wording "*inducing or stimulating*" in claim 1 of the

patent is broader than the term "*enhancing*" used on page 12, lines 23 to 25 of the application as filed, is immaterial, because an isolated oligonucleotide agent having the structural features specified in claim 1, for use in a method of immunotherapy to stimulate or induce an immune response can be derived directly and unambiguously from, *inter alia*, page 1, lines 10 to 13; page 6, lines 8 to 16; page 5, lines 18 to 20, and page 1, lines 10 to 13, as well as claims 1, 2, 10 and 11 of the application as filed.

5. As regards the subject-matter of claim 2, the board shares the opposition division's view that a person skilled in the art can derive from the passage on page 15, lines 11 to 16 not only an *in vivo*, but also an *in vitro* method of stimulating an immune response in a cell using an oligonucleotide agent of the invention. The question of whether the claimed oligonucleotide agents can stimulate an immune response *in vitro* in each type of cells, might be relevant in connection with the ground for opposition of Article 100(b) EPC, but is immaterial to the assessment whether the subject-matter of claim 2 extends beyond the content of the application as filed.

6. The appellant objected to claims 14 and 15 under Article 100(c) EPC for the same reason given for claim 1, namely the alleged lack of basis in the application as filed for a method of immunotherapy by inducing an immune response in a mammal. In view of the disclosure on page 1, lines 10 to 13 of the application as filed, the objection is not justified.

7. Since appellant's objection to claims 3 to 9, 16 and 19 was based solely on the direct or indirect reference to independent claims 1 and 2 therein, the same reasons

given for those claims apply (see paragraphs 4 and 5 above).

8. Hence, the ground for opposition of Article 100(c) EPC does not prejudice the maintenance of the patent as granted.

Article 100(b) EPC

9. The appellant contested the opposition division's finding that the disclosure in the patent enables a person skilled in the art to carry out the invention over the whole scope of claims 1, 2 and 10.

Claim 1

10. Claim 1 is a second medical use claim in the format of a purpose-restricted product claim pursuant to Article 54(5) EPC, which is directed to an isolated oligonucleotide agent for use in a method of immunotherapy by inducing or stimulating an immune response.

11. Contrary to the view taken by the appellant, there is no requirement for a purpose-restricted product claim pursuant to Article 54(5) EPC to recite a disease or pathological condition. According to Article 54(5) EPC, patentability of substances or compositions comprised in the state of the art for any specific use in a method referred to in Article 53(c) EPC is not excluded, provided that such use is not comprised in the state of the art as defined in Article 54(2) (3) EPC. Article 53(c) EPC refers to, *inter alia*, methods for treatment of the human or animal body by surgery or therapy. The meaning of the term "therapy" in Article 53(c) EPC is not restricted to curing or

preventing a particular disease. Rather, the term covers any treatment which is designed to cure, alleviate, remove or lessen the symptoms of, or prevent or reduce the possibility of contracting any disorder or malfunction of the human or animal body (see decision T 24/91, OJ EPO 1995, 512; point 2.7 which relates to the term "therapy" in Article 54(2) EPC 1973).

12. Further, the appellant contested the opposition division's adverse findings on sufficiency of disclosure arguing that claim 1 is unduly broad, and that the therapeutic effect specified therein cannot be plausibly achieved over the whole scope of the claim.

13. According to the established case law of the Boards of Appeal, the mere fact that a claim is broad is not in itself a ground for considering that the requirement of sufficient disclosure in the patent is not met (see, *inter alia*, decision T 19/90, OJ EPO 1990, 476, point 3.3; and decision T 636/97 of 26 March 1998, point 4.5). For claims directed to a second medical use, it has been established in the case law that the requirement of sufficient disclosure is usually fulfilled if a person skilled in the art can obtain the therapeutic agent to be applied, and the patent renders it plausible that the therapeutic agent is suitable for the claimed therapeutic application (see decision T 1959/15 of 2 April 2020, point 4.2). Clinical data may not be required, if the patent provides information in the form of experimental tests showing an effect which, for the skilled person, directly and unambiguously reflects the therapeutic application (see decision T 241/95, OJ EPO 2001, 103, point 4.1.2; and decision T 158/96 of 28 October 1998, point 3.5.2).

14. In the present case, the appellant did not explicitly dispute that an isolated oligonucleotide agent characterized by the structural features specified in claim 1 could be obtained. While in the context of the validity of the priority the appellant contended that the two structural features defining the oligonucleotide agents of claim 1 could not be technically reconciled, this would be, if anything, a clarity issue which cannot be considered by the board (see decision G 3/14, OJ EPO 2015, 102).

15. The present patent provides ample experimental evidence for the suitability of the oligonucleotide agents of claim 1 for immunotherapy by inducing or stimulating an immune response. Two oligonucleotides (TLR9.1 and TLR9.2) comprising the sequence of SEQ ID NO:1 are shown in the patent to induce the production of IFN-α in human plasmocytoid dendritic cells (PD cells) *in vitro* (see paragraph [0141] and Figure 2). As apparent from Figure 3B, also oligonucleotides L8A, L9A, L10A and DR comprising the sequence of SEQ ID NO:1 (see Table 2 of the patent) show an immunostimulatory effect *in vitro*.

16. As regards the immune response *in vivo*, the patent provides experimental evidence that the TLR9.2 duplex and the TLR9.2 sense strand, each comprising the sequence of SEQ ID NO:1, show the highest activity to induce systemic levels of IFN-α and to activate CD4 and CD8 T cells and myeloid dendritic cells (see Figure 5). The data obtained in mice are said to be consistent with the *in vitro* data in both the human and the murine system (see paragraphs (0149] and [0150]).

17. Moreover, the patent discloses that production of IFN-α in human PD cells *in vitro* is induced also by

oligonucleotides R3A and R4A (see Figure 3B). Oligonucleotides R3A and R4A comprise a sequence which differs from SEQ ID NO:1 in, respectively, 1 and 2 nucleotides and includes, respectively, 6 and 5 contiguous nucleotides taken from the 5' end of SEQ ID NO:1 (see Table 2).

18. The efficacy in (a) inducing IFN-α production, both *in vitro* in human PD cells and *in vivo* in mice, and (b) activating CD4 and CD8 T cells and myeloid dendritic cells *in vivo*, directly and unambiguously reflects the technical effect specified in claim 1, namely inducing or stimulating an immune response. Hence, having regard to the experimental data provided in the patent and the common general knowledge at the relevant date, a person skilled in the art would consider plausible that the oligonucleotide agents referred to in claim 1 are suitable to achieve a therapeutical effect in a method of immunotherapy by inducing or stimulating an immune response.

19. Appellant's arguments concerning the alleged lack of suitability of oligonucleotides shorter or longer than 19 nucleotides for immunotherapy are not persuasive. It is apparent from Figure 3B of the patent that two oligonucleotides (a 12mer and a 16mer) comprising the sequence of SEQ ID NO:1 show a **lower** activity in inducing IFN-α production *in vitro* than the 19mer oligonucleotide, but their immunostimulatory activity is not completely abolished. Thus, a therapeutical effect cannot be excluded for oligonucleotides according to the invention which are shorter than the 19mers exemplified in the patent because, as shown in document (11), even a 5mer RNA oligonucleotide may potentially have immunostimulatory activity.

20. Appellant's further allegation that oligonucleotides longer than the 19mers exemplified in the patent would not be suitable for immunotherapy was not substantiated by verifiable facts (see, *inter alia*, decision T 19/90, OJ EPO 1990, 476).

21. The appellant took the view that the patent does not provide the skilled person with sufficient guidance on the issue of nucleotide modifications. The board disagrees. As a matter of fact, the patent clearly discloses modified nucleotides which impair the immunostimulatory activity of the claimed oligonucleotides and other modifications which do not (see paragraphs [0147], [0170] and [0171] and Figure 4B of the patent). In particular, it is stated in the first sentence of paragraph [0171]:

> "*Hence, if it seems desirable to modify an immunostimulatory oligonucleotide of the invention, e.g. in order to protect it against nucleolytic degradation, this may be achieved by introducing 2'-fluoro modifications, and preferably introducing these modifications in such a manner that the nucleotides of SEQ ID NO:1 remain unmodified*".

22. Also appellant's objection concerning the lack of plausibility of an immunostimulatory effect for DNA oligonucleotides is without merit. The statements on page 18, lines 8 and 9 of document (11) on which the appellant relied ("*It has now been surprisingly discovered by the inventors that certain G,U-containing RNA molecules and their analogues, but not their DNA counterparts, are immunostimulatory*"), relate to the DNA counterparts of particular G,U-containing RNAs. It cannot be derived from these statements that DNA oligonucleotides in general are not immunostimulatory.

More importantly, even though the oligonucleotide agent of claim 1 is not explicitly characterized as a RNA oligonucleotide, it is required to comprise the sequence of SEQ ID NO:1 (5' G**U**CC**UU**CAA 3') or a sequence derived therefrom which comprises at least four contiguous nucleotides taken from the 5' end of this sequence, which is, undoubtedly, a RNA sequence.

23. The board shares the opposition division's view that, while the structural features in claim 1 may apply to a large number of oligonucleotides, the functional feature that the oligonucleotide agent must be suitable for immunotherapy by inducing or stimulating an immune response restricts the scope of the claim to a limited number of oligonucleotides. As the opposition division held, candidate oligonucleotides having the structural features specified in claim 1 can be tested for their activity in inducing or stimulating an immune response by *in vitro* and *in vivo* methods disclosed in the patent or known in the art at the relevant date. Carrying out such routine tests to find further oligonucleotide agents as defined in claim 1 does not involve undue burden. Contrary to appellant's view, neither a full screen of **all** the oligonucleotides having the structural features specified in claim 1, nor a research program are required for carrying out the invention as claimed.

24. Finally, it should be noted that the question of whether or not a skilled person is working within the scope of the claim is not related to sufficiency of disclosure, but to the definition of the scope of the claim (see, *inter alia*, decision T 1811/13 of 8 November 2016). Also the question of whether future inventions may fall under the scope of the claim is immaterial to the assessment of sufficiency of

disclosure, because otherwise no dominant patent could exist (see also decision T 292/85, point 3.1.2).

25. For these reasons, the board cannot endorse appellant's objection that the invention is not sufficiently disclosed over the whole scope of claim 1.

Claim 2

26. Claim 2 relates to an *in vitro* method of stimulating an immune response in a cell, comprising the step of administering to said cell an oligonucleotide agent as defined in claim 1.

27. While it is undisputed that the patent discloses an *in vitro* method in which the claimed oligonucleotide is administered to human PD cells, the appellant contended that the patent does not provide any guidance on other types of cells suitable for carrying out the method of claim 2.

28. The board disagrees. As apparent from the evidence on file, it was known in the art that immunostimulatory activity can be tested *in vitro* in a variety of cell types, e.g. peripheral lymphocytes from cow blood (see document (17)), murine spleen cells from DBA/2 mice, murine B lymphoma WEHI-231 cells and murine monocyte J774 cells (see document (18)). The present patent discloses that IFN-α induction by the oligonucleotide agents of the invention requires the presence of a TLR7 receptor in the cell (see paragraphs [0151] and [0152]). Hence, a person skilled in the art derives from this disclosure that cells expressing the TLR7 receptor are required for carrying out the *in vitro* method of claim 2. In the absence of evidence that such cells were not available at the

relevant date, or that obtaining or using them involved undue burden, the objection to claim 2 is not justified.

29. The reasons given above for claims 1 and 2 apply, *mutatis mutandis*, to the claims of the patent which refer, directly or indirectly, to those claims, or in which oligonucleotides are defined by the same structural features specified in claim 1.

Claim 10

30. Claim 10 relates to a method of making an oligonucleotide agent so as to avoid stimulating an immune response in a mammal, the method comprising the step of eliminating from an agent pool any agent comprising a sequence as defined in the claim.

31. In the decision under appeal, the opposition division held that techniques for excluding specific oligonucleotides from a pool of oligonucleotides were part of the common general knowledge of a person skilled in the art at the relevant date. This finding was contested by the appellant arguing that the phrasing of claim 10 remains obscure, and that eliminating a specific oligonucleotide from an oligonucleotide pool was not at all common general knowledge at the relevant date.

32. The board does not share appellant's views. It is clear from the wording of claim 10 that the purpose of the claimed method is to obtain an oligonucleotide agent which does **not** induce an immune response in a mammal. The claimed method is particularly suited for preparing oligonucleotide agents which specifically inhibit the expression of target genes by a mechanism known as RNA

interference (see paragraphs [0002] to [0004] of the patent), because for such agents the immunostimulatory effect of the sequence motif defined in claim 10 would be undesirable.

33. Like the opposition division, the board considers that, at the relevant date, specific hybridization to complementary DNA oligonucleotide probes attached to a solid support was a standard technique for isolating specific DNA or RNA molecules, including oligonucleotides from a mixture, and that the skilled person could retrieve the required technical guidance from laboratory manuals.

34. Specific hybridization was, however, not the sole technique that the skilled person would have contemplated for carrying out the method of claim 10. As the opposition division indicated in the decision under appeal, excluding specific oligonucleotides from a pool of oligonucleotides is a straightforward design task in the process of preparing a desired oligonucleotide pool by chemical synthesis, which was the standard technique for making oligonucleotides at the relevant date. As a matter of fact, this task was performed by laboratory technicians in daily work, and did not involve undue burden nor require inventive skills.

35. For these reasons, the objection of lack of sufficient disclosure of the method of claim 10 is not justified.

Priority (Article 87 EPC)

36. In the decision under appeal, the opposition division found that priority rights from the earlier

US application filed on 9 December 2004 may be validly claimed.

37. The appellant did not dispute that the priority application discloses an oligonucleotide agent consisting of, or comprising a sequence differing by not more than 2 nucleotides from SEQ ID NO:1 (see claim 3 of the priority application) and an embodiment characterized by the feature "*4, 5, 6, 7 or 8 or more contiguous nucleotides are taken from the 5' end of SEQ ID NO: 1*" (see page 5, lines 6 to 9, and the paragraph bridging pages 9 and 10). However, it contended that these disclosures relate to distinct embodiments, and that the priority application does not provide a pointer towards a combination of the two embodiments as in claim 1 of the patent as granted.

38. Like the opposition division in the decision under appeal, the board regards the results of the experiments disclosed in the passage on page 35, lines 13 to 24 of the priority application as a pointer to the combination of the structural features disclosed in, respectively, claim 3 and the passage on page 5, lines 6 to 9.

39. The passage on page 35 discloses that the 9 bases at the 3' end of the sense strand of the TLR9.2 oligonucleotide are responsible for the immunostimulatory activity of the oligonucleotide (see lines 20 and 21). The fact that this passage does not refer to a "SEQ ID NO:1" is immaterial because, as derivable from page 5, line 5 or page 9, line 27 of the priority application, the 9 bases at the 3' end of the sense strand of TLR9.2 (5' GUCCUUCAA 3') correspond precisely to SEQ ID NO:1.

40. As stated in the decision under appeal, a person skilled in the art derives from the results of the experiments described on page 35 that, in order for the oligonucleotide to be active, at least the first four nucleotides at the 5' end of SEQ ID NO:1 have to be maintained. While there is no explicit statement to this effect in the priority application, the teaching is directly and unambiguously derivable from the passage on page 35, lines 21 to 24 which reads:

> "*The exchange of increasing numbers of bases in this 9mer sequence resulted in a gradually decreasing immunological activity of the sense strand of TLR9.2 with a complete loss of activity when six bases were exchanged within the 9mer sequence (Fig. 3B, R8A)*"

As apparent from Figure 3B referred to in this passage, oligonucleotides R5A, R4A, R3A, 19U and 18/18UU induced production of IFN-α in human PDCs at levels that amount to at least half of the level induced by the TLR9.2 oligonucleotide ("n" in Figure 3B). In the R5A, R4A, R3A, 18/18UU and 19U oligonucleotides, 4, 5, 6, 7 and 8 contiguous nucleotides from the 5' end of SEQ ID NO:1 are maintained (see Table 2 and the passage on page 5, lines 8 and 9 disclosing the sequences at the 5' end of the respective modified motifs). Except for the R5A oligonucleotide, each of the exemplified oligonucleotides comprises a sequence that differs from SEQ ID NO:1 by 1 or 2 nucleotides, as required by claim 3 of the priority application.

41. Contrary to appellant's view, there is no inconsistency between the structural features disclosed, respectively, in claim 3 and on page 5, lines 6 to 9. It is immediately apparent to a skilled person reading

the priority application as a whole that the need to maintain at least 4 contiguous nucleotides taken from the 5' end of SEQ ID NO:1 as disclosed on page 5, lines 6 to 9 limits the degree of sequence variability allowed by claim 3, insofar as it excludes nucleotide exchanges at least in those 4 contiguous nucleotides.

42. The reasons given above apply also to the claims of the patent as granted that either refer to claim 1, or include the combination of the two structural features at issue. Since the appellant objected to the validity of the priority right by referring to the arguments put forward in connection with Article 100(c) EPC, *mutatis mutandis* also the reasons given in paragraphs 4 to 7 above apply.

43. In summary, the board concurs with the opposition division in that the priority rights from the earlier US application are validly claimed. Hence, document (8) published after the priority date does not form part of the state of the art for the assessment of novelty and inventive step.

Admission of documents (19) and (19a) into the proceedings (Article 12(4) RPBA)

44. Exercising the discretion conferred to the board by Article 12(4) of the Rules of Procedure of the Boards of Appeal (RPBA) 2007, applicable to the present case by virtue of Article 25 RPBA 2020, documents (19) and (19a), filed as documents (16) and (16a) together with appellant's statement of grounds of appeal, were not admitted into the proceedings. The appellant did not put forward any arguments as to why these documents could not have been presented in opposition

proceedings, and the board is not aware of any circumstances which may justify their late filing.

Novelty (Article 54 EPC)

45. Since there is no document on file which anticipates the claimed subject-matter, novelty is acknowledged.

Inventive step (Article 56 EPC)

46. In the decision under appeal, the opposition division found that, starting from document (9) as the closest state of the art, the problem to be solved is "... *the provision of further immunostimulatory oligonucleotides for use in a method of immunotherapy, and of methods and products related to*". In the light of documents (10) and (11), the solution provided by the subject-matter of claim 1 was considered to involve an inventive step.

47. Document (9) addresses the same technical problem as the present invention, namely the provision of methods and means for inducing or stimulating an immune response. It describes that production of IFN-α in PD cells is induced in response to wild-type influenza virus and polyuridylic acid (poly(U)) (see Figure 3A and 3B). Induction of IFN-α is said to require endosomal recognition of the RNA and signalling by means of Toll-like receptor 7 (TLT7) and MyD88 (see abstract).

48. The authors of document (9) state that, although they do not exclude the possibility that TLR7 has a preference for a particular RNA motif, the fact that it mediates responses to poly(U) suggests that this motif is very simple. Since some short ssRNA oligonucleotides

(of the type used for making short interfering dsRNA) also induce IFN-α production, the authors suggest that endosomal delivery of ssRNA could be exploited as an adjuvant for vaccination and immunotherapy (see last sentence of the paragraph bridging the middle and the right-hand column on page 1531).

49. In particular, two specific RNA oligonucleotides, RNA oligo 1 and RNA oligo 2, are tested for induction of IFN-α and the results are shown in Figure 3E. The RNA oligo 1 comprises a nucleotide sequence representing positions 2 to 6 of SEQ ID NO:1, namely UCCUU, but RNA oligo 2 is structurally unrelated to the oligonucleotides of the present invention. As apparent from Figure 3E of document (9), only RNA oligo 2 induced the production of IFN-α in PD cells.

50. However, the appellant chose the RNA oligo 1 as the starting point for the analysis of inventive step applying the problem-solution approach. This approach is misguided because the RNA oligo 1, even though structurally similar to the oligonucleotide agents claimed in the patent, does not show any immunostimulatory activity. Thus, it is difficult to see why a skilled person would consider RNA oligo 1 as a promising starting point for providing immunostimulatory oligonucleotides suitable for immunotherapy. In the board's view, an objection of lack of inventive step based on the clearly ineffective RNA oligo 1 as the closest state of the art is necessarily tainted with hindsight, since the choice of this oligonucleotide can only be motivated by previous knowledge of the claimed invention.

51. This deficiency cannot be remedied by the teachings of document (10) or document (11) relating to the same technical field as the present invention.

52. Document (10) describes that GU-rich RNA oligonucleotides of various lengths (e.g. 10mer RNA33, 5' GUAGUGUGUG and 12mer RNA34, 5' GUCUGUUGUGUG; see page 1527, left-hand column, lines 10 to 18 of the first full paragraph) stimulated PD cells to produce IFN-α. The authors suggest that the use of synthetic GU- or U-rich RNA oligonucleotides "*... may be fundamental to the generation of powerful new adjuvants for vaccination and immunotherapy*" (see page 1528, last sentence in the right-hand column).

53. As stated by the opposition division in the decision under appeal, the immunostimulatory motif of SEQ ID NO:1 can hardly be regarded as a GU- or U-rich sequence. Moreover, uracil "enrichment" of this motif does not seem to result in an increased IFN-α induction. Compare the amount of IFN-α induced by oligonucleotide "n" with that induced by oligonucleotide 18/19UU in Figure 3B of the present patent, the two oligonucleotides being identical except that in the latter the two adenines at the 3' end of SEQ ID NO:1 have been replaced by two uracils.

54. The teaching of document (11) that RNA and RNA-like molecules containing guanine (G) and uracil (U) are immunostimulatory (see page 17, lines 24 to 26) is rather speculative and not supported by the experimental results provided in the same document. Comparing the results using oligonucleotide CUAGGCAsC (1 uracil and 2 guanines, no GU-sequence) with those using oligonucleotide GUGUUUAsC (2 guanines, 4 uracils, 2 GU-sequences) in Figure 2 of document (11), it

appears that higher G, U or GU contents do not necessarily correlate with a higher IFN-α induction.

55. Like the opposition division, the board is unable to find in the teachings of documents (9), (10) and (11), either alone or in combination, a clear indication guiding the skilled person towards the specific immunostimulatory motif of SEQ ID NO:1 or variants thereof as defined in claim 1. The same applies with respect to claims 2 to 9, 11 to 16 and 19.

56. The question of whether the claimed oligonucleotide agents are suitable for use in a method of immunotherapy by inducing or stimulating an immune response was answered to the affirmative earlier in this decision in the context of sufficiency of disclosure. Thus, contrary to the view taken by the appellant, the board is persuaded that the claimed oligonucleotide agents and methods plausibly solve the problem as formulated by the opposition division, namely the provision of further immunostimulatory oligonucleotides for use in a method of immunotherapy, and of methods and products related thereto.

57. Hence, the objection of lack of inventive step is not justified.

Conclusion

58. The arguments put forward by the appellant in appeal proceedings fail to persuade the board that any of the grounds of opposition of Article 100 EPC prejudices the maintenance of the patent as granted. Thus, appellant's request to set aside the decision under appeal cannot be granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated