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Datasheet for the decision of 2 November 2021

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Application Number:	07801562.5
Publication Number:	2056845
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Language of the proceedings:	EN

Title of invention:
STRUCTURE AND USE OF 5' PHOSPHATE OLIGONUCLEOTIDES

Patent Proprietor:
Rheinische Friedrich-Wilhelms-Universität Bonn

Opponent:
Withers & Rogers LLP

Headword:
5' Phosphate oligonucleotides / RHEINISCHE FRIEDRICH-WILHELMS-UNIVERSITÄT BONN

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Relevant legal provisions:
EPC Art. 54, 56, 100(c), 123(2)
RPBA Art. 12(4)

Keyword:
Novelty - main request, auxiliary requests 1 and 2 (yes)
Inventive step - main request, auxiliary requests 1 and 2 (no)
Amendments - added subject-matter - auxiliary requests 3 to 15 (yes)

Decisions cited:
G 0002/10, T 1621/16

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Case Number: T 0446/20 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 2 November 2021

Appellant: (Patent Proprietor)	Rheinische Friedrich-Wilhelms-Universität Bonn Regina-Pacis-Weg 3 53113 Bonn (DE)
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Representative:	Graf von Stosch, Andreas Graf von Stosch Patentanwaltsgesellschaft mbH Prinzregentenstraße 22 80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 12 December 2019 concerning maintenance of the European Patent No. 2056845 in amended form**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	S. Albrecht
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 2 056 845 ("the patent") is based on European patent application No. 07 801 562.5 ("application as filed"). The patent was granted on the basis of a set of seven claims.

Claim 1 as granted reads as follows:

"1. An oligonucleotide capable of inducing a type I IFN production for use in inducing apoptosis of tumor cells through binding to RIG-I in the treatment of a tumor in a vertebrate animal,
wherein the oligonucleotide comprises at least 1, preferably at least 3, more preferably at least 6 ribonucleotide(s) at the 5' end,
wherein the oligonucleotide comprises a triphosphate group at the 5' end, and wherein the triphosphate group is free of any cap or modification,
wherein the oligonucleotide is at least 21 nucleotides in length, and
wherein the oligonucleotide is a ligand of RIG-I."

II. Opposition proceedings were based on the grounds for opposition under Article 100(a) EPC for lack of novelty and lack of inventive step and under Article 100(b) and (c) EPC.

III. The documents filed during the opposition proceedings included:

D1: US 2006/0178334 A1
D2: WO 2005/005632 A2

D4: M. Schlee *et al.*, "siRNA and isRNA: Two Edges of One Sword", Molecular Therapy 14(4), published online 31 July 2006, 463-70
D6b: WO 2006/063252 A2
D12: M. Chawla-Sarkar *et al.*, "Apoptosis and interferons: Role of interferon-stimulated genes as mediators of apoptosis", *Apoptosis 8,* 2003, 237-49
D19: B. Scheel *et al.*, "Therapeutic anti-tumor immunity triggered by injections of immunostimulating single-stranded RNA", Eur. J. Immunol. 36, 2006, 2807-16
D25: J. Trindade Marques *et al.*, "A structural basis for discriminating between self and nonself double-stranded RNAs in mammalian cells", Nature Biotechnology 24(5), May 2006, 559-65

IV. The opposition division decided that the patent in amended form in the version of auxiliary request 3 and the invention to which it related met the requirements of the EPC. The decision was based on a main request and on sets of claims of three auxiliary requests. The main request was the patent as granted. The opposition division concluded that claim 1 of the main request, auxiliary request 1 and auxiliary request 2 comprised added subject-matter (Article 100(c) EPC).

V. The patent proprietor ("appellant-patent proprietor") and the opponent ("appellant-opponent") each lodged an appeal against the opposition division's decision.

VI. With its statement of grounds of appeal, the appellant-patent proprietor requested as a main request that the decision under appeal be set aside and that the patent be maintained as granted, implying that the opposition be rejected, or, alternatively, that the patent be maintained in amended form on the basis of

one of the sets of claims of auxiliary requests 1 and 2 underlying the impugned decision. Claim 1 of each of these two requests is identical to claim 1 as granted.

VII. With its statement of grounds of appeal, the appellant-opponent requested that the decision under appeal be set aside and that the patent be revoked in its entirety. The appellant-opponent also submitted, *inter alia*, new documents, numbered as D32 to D36.

VIII. With its reply to the appellant-opponent's statement of grounds of appeal, the appellant-patent proprietor filed sets of claims of auxiliary requests 3 to 15 and submitted new documents, numbered D37 to D41.

Claim 1 of each of auxiliary requests 3 to 5 differs from claim 1 as granted in that the medical use is defined as follows (added features underlined):

- "for use in directly inducing apoptosis of tumor cells through binding to RIG-I in the treatment of a tumor in a vertebrate animal" (claim 1 of auxiliary request 3)

- "for use in mediating a direct anti-tumor effect by inducing apoptosis of tumor cells through binding to RIG-I in the treatment of a tumor in a vertebrate animal" (claim 1 of auxiliary request 4)

- "for use in inducing apoptosis of tumor cells in an IFN-independent manner through binding to RIG-I in the treatment of a tumor in a vertebrate animal" (claim 1 of auxiliary request 5)

Claim 1 of each of auxiliary requests 6 to 8 is identical to claim 1 as granted with the exception that

the oligonucleotide must be an RNA oligonucleotide and that the feature "wherein the oligonucleotide comprises at least 1, preferably at least 3, more preferably at least 6 ribonucleotide(s) at the 5' end" has been deleted.

Claim 1 of each of auxiliary requests 9 to 11 is identical to claim 1 of auxiliary requests 3 to 5 respectively with the exception that the oligonucleotide must be an RNA oligonucleotide and that in auxiliary requests 9 and 10 the feature "wherein the oligonucleotide comprises at least 1, preferably at least 3, more preferably at least 6 ribonucleotide(s) at the 5' end" has been deleted.

Claim 1 of each of auxiliary requests 12 and 13 differs from claim 1 of auxiliary requests 10 and 11 respectively in that the oligonucleotide has been specified to have gene silencing activity and that in auxiliary request 13 the feature "wherein the oligonucleotide comprises at least 1, preferably at least 3, more preferably at least 6 ribonucleotide(s) at the 5' end" has been deleted.

Claim 1 of each of auxiliary requests 14 and 15 differs from claim 1 of auxiliary requests 12 and 13 respectively in that the oligonucleotide has been specified to have Bcl-2 gene silencing activity.

IX. The board issued a summons to oral proceedings in accordance with the requests of the parties.

X. In a communication pursuant to Article 15(1) RPBA issued on 5 October 2021, the board drew the parties' attention to the points to be discussed during the oral proceedings and gave a preliminary opinion on the

interpretation of the claimed feature "for use in inducing apoptosis of tumor cells through binding to RIG-I".

XI. In a letter dated 6 October 2021, the appellant-patent proprietor requested that the oral proceedings be conducted by videoconference.

XII. In a letter dated 19 October 2021, the appellant-opponent informed the board that it would not be attending the oral proceedings.

XIII. Oral proceedings took place as videoconference in the absence of the appellant-opponent. At the end of the oral proceedings, the Chairwoman announced the board's decision.

XIV. The appellant-patent proprietor's written and oral case relevant for the present decision may be summarised as follows.

Main request, auxiliary requests 1 and 2 - claim 1 - interpretation of the feature "for use in inducing apoptosis of tumor cells through binding to RIG-I"

This feature required a direct apoptotic effect on the tumour cells, i.e. an effect which did not involve binding of the claimed oligonucleotides to RIG-I and subsequent induction of type I IFN production.

Main request, auxiliary requests 1 and 2 - claim 1 - novelty

Document D1 failed to disclose, explicitly or implicitly, the new technical effect of 5'-triphosphate RNA of inducing IFN-independent apoptosis of tumour cells through binding to RIG-I in the treatment of

tumour. Rather, document D1 disclosed that IFN could induce apoptosis of virus-infected cells.

Main request, auxiliary requests 1 and 2 - claim 1 - inventive step

In contrast to document D25, document D1 did not constitute a suitable starting point for the assessment of inventive step.

Even if document D1 were taken as the closest prior art, it did not render the claimed subject-matter obvious, neither by itself nor in combination with any other prior-art document relied on by the appellant-opponent.

Document D1 failed to disclose that the oligonucleotides it described were ligands of RIG-I and that these induced apoptosis of tumour cells through binding to this receptor. The technical effect associated with these differences was twofold in that the claimed oligonucleotides achieved a direct, IFN-independent tumour cell apoptosis in addition to inducing IFN-dependent tumour cell apoptosis, as evidenced by Examples 11 and 12 of the patent.

Accordingly, the objective technical problem to be solved by the claimed invention was the provision of oligonucleotides which exhibited an improved anti-tumour response in a vertebrate animal, comprising a direct anti-tumour cytotoxic effect. The proposed solution, i.e. oligonucleotides in accordance with claim 1, was inventive since no prior-art document relied on by the appellant-opponent contained any pointer towards the direct, IFN-independent apoptotic

effect of the claimed oligonucleotides demonstrated in the patent.

Auxiliary request 3 - claim 1 - amendments (Article 123(2) EPC)

The subject-matter of this claim was directly and unambiguously derivable from the following passages of the application as filed:

(a) page 17, lines 5 to 13 and 27
(b) page 23, lines 16 to 19, 28 to 31
(c) page 36, lines 20 to 28
(d) page 59, lines 7 to 31
(e) page 63, lines 8 to 13
(f) page 101, lines 33 to 34
(g) page 102, lines 16 to 19
(h) page 103, lines 1 to 12
(i) Figure 16 in conjunction with page 12, lines 26 to 27

Specifically, the claimed oligonucleotides were described on page 36, lines 20 to 28 of the application as filed. The passage on page 63, lines 8 to 13 of the application as filed, in turn, disclosed that the oligonucleotides of the invention, their precursors and bacterial RNA, may exert certain functions such as inducing tumour cell apoptosis through binding to RIG-I.

From the application as filed - notably the claims, the summary of the invention on page 5, lines 1 to 11 and Examples 1 to 7, 12, 13 and 15 - the skilled reader would have understood that the claimed oligonucleotides were preferred over bacterial RNA.

Pointers to the combination of the claimed induction of apoptosis through binding to RIG-I and the oligonucleotides' capability of inducing type I IFN induction were provided on page 23, lines 16 to 19 and page 59, lines 7 to 31 of the application as filed.

XV. The appellant-opponent's written case relevant for the present decision may be summarised as follows.

Main request, auxiliary requests 1 and 2 - claim 1 - interpretation of the feature "for use in inducing apoptosis of tumor cells through binding to RIG-I"

Neither the wording of claim 1 itself nor the application as filed provided any basis for the appellant-patent proprietor's limited interpretation of this feature. This feature merely required that the claimed oligonucleotides bind to RIG-I and that this binding lead - by whatever means - to the induction of tumour cell apoptosis. As a consequence, the claimed medical use did not only include the direct induction of tumour cell apoptosis through binding of the claimed oligonucleotides to RIG-I, but also the indirect activation of tumour cell apoptosis through binding of the claimed oligonucleotides to RIG-I and subsequent induction of type I IFN production.

Main request, auxiliary requests 1 and 2 - claim 1 - novelty and inventive step

The claimed subject-matter lacked novelty over document D1.

If novelty of the claimed subject-matter over document D1 were nonetheless acknowledged, the claimed invention would have been obvious in light of this document in

combination with the common general knowledge disclosed in document D12 that type I IFN induced apoptosis of tumour cells.

Main request, auxiliary requests 1 and 2 - amendments (Article 100(c) EPC; Article 123(2) EPC)

The feature of claim 1 "for use in inducing apoptosis of tumor cells through binding to RIG-I" was not directly and unambiguously derivable from the application as filed. Solely the passage on page 63, lines 8 to 13 of the application as filed disclosed the required relationship between binding to RIG-I and induction of apoptosis of tumour cells as one of numerous possible functions. The same paragraph disclosed oligonucleotides as one of three alternative embodiments. The claimed feature "for use in inducing apoptosis of tumor cells through binding to RIG-I" thus amounted to a selection out of two lists and was therefore not in line with the requirements of Article 100(c) EPC (main request) and Article 123(2) EPC (auxiliary requests 1 and 2).

XVI. The parties' final requests relevant to the present decision were as follows.

The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained as granted, implying that the opposition be rejected (main request), or, alternatively, that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 and 2 underlying the impugned decision or one of the sets of claims of auxiliary requests 3 to 15, all filed with the reply to the appellant-opponent's statement of grounds of appeal.

The appellant-patent proprietor further requested that documents D37 to D41 be admitted into the appeal proceedings and that documents D31 to D36 not be admitted into the appeal proceedings.

The appellant-opponent requested in writing that the decision under appeal be set aside and that the patent be revoked in its entirety, that documents D32 to D34 be admitted into the appeal proceedings, and that the appellant-patent proprietor's appeal be dismissed.

Reasons for the Decision

1. The appeals are admissible.

2. Admittance of documents D31 to D36 and D37 to D41 (Article 12(4) RPBA)

2.1 The appellant-patent proprietor filed documents D37 to D41 in direct reply to the appellant-opponent's filing of documents D31 to D36.

2.2 In the oral proceedings, the board decided not to admit documents D31 to D36 into the proceedings. As a consequence, documents D37 to D41 were not admitted into the proceedings either. As none of these documents turned out to be relevant for the present decision, the decision to not admit them into the proceedings does not require further reasoning.

Main request (patent as granted)

3. Background of the claimed invention

3.1 Claim 1 is a purpose-restricted product claim drawn up in accordance with Article 54(5) EPC.

3.1.1 The product is an oligonucleotide characterised, *inter alia*, by the fact that it is capable of inducing type I IFN production and that it is a ligand of RIG-I.

3.1.2 The claimed purpose, in turn, is the induction of apoptosis of tumour cells through binding to RIG-I in the treatment of a tumour in a vertebrate animal.

3.2 At the effective date of the patent, the following facts on RIG-I formed part of the state of the art (see background art discussed in paragraphs [0005] to [0009] of the patent and document D4, Figure 1 in conjunction with page 464, right-hand column, first full paragraph, lines 20 to 26).

(a) RIG-I is a cytosolic protein receptor expressed in both immune and non-immune cells.

(b) RIG-I takes part in nucleic acid recognition.

(c) The signalling pathway of RIG-I involves recruitment of a CARD-containing adaptor, IPS-1 (also known as MAVS, VISA or Cardif). IPS-1 relays the signal to the kinases TBK1 and IKK-i, which phosphorylate interferon-regulatory factor-3 ("IRF")-3 and IRF-7, i.e. transcription factors essential for the expression of type I interferons.

3.3 In view of these undisputed facts, the board is satisfied that binding of the claimed oligonucleotides to RIG-I leads to induction of type I IFN production in immune and non-immune cells.

4. Claim construction - interpretation of the feature "inducing apoptosis of tumor cells through binding to RIG-I" recited in claim 1 ("feature A")

4.1 The parties adopted different interpretations of feature A. In the appellant-patent proprietor's view, this feature required a direct apoptotic effect on tumour cells which did not involve binding of the claimed oligonucleotides to RIG-I and subsequent induction of type I IFN production. By contrast, the appellant-opponent interpreted this feature as encompassing the indirect activation of tumour cell apoptosis through binding of the claimed oligonucleotides to RIG-I and subsequent induction of type I IFN production.

4.2 It is a well-established principle laid down by the boards' case law that a non-specific definition in a claim should be given its broadest technically sensible meaning.

4.3 In the case in hand, there is no doubt that the appellant-patent proprietor's interpretation of feature A makes technical sense.

4.4 In the board's judgement, the same holds true for the appellant-opponent's interpretation of this same feature. The link between binding of the claimed oligonucleotides to RIG-I and induction of type I IFN production is well established in the prior art (see points 3.2 and 3.3 above). The ability of type I IFN to induce apoptosis in several cancer cell lines is likewise common general knowledge (see document D12, page 239, right-hand column, first and second full paragraphs; page 245, Figure 4).

4.5 The board did not overlook that type I interferons elicit pleiotropic biological effects (see document D12, abstract). Moreover, it appears undisputed that document D12 suggests several mechanisms of action by which type I interferons exert their anti-tumour activity including mechanisms unrelated to apoptosis of tumour cells (see Table 2). However, this does not render the appellant-opponent's interpretation of feature A not technically sensible.

4.6 In the oral proceedings, the appellant-patent proprietor put emphasis on the fact that type I IFN-induced tumour cell apoptosis via activation of RIG-I was a systemic event occurring late in time (i.e. after 48 hours of treatment), as evidenced by document D12, page 239, right-hand column, last paragraph. By contrast, RIG-I induced tumour cell apoptosis as claimed took place within 24 hours only, as shown in Example 12 of the patent. Furthermore, the patent itself disclosed in paragraphs [0042], [200], [201], [205] and [217] type I IFN induction and RIG-I induced tumour cell apoptosis as separate, distinct anti-tumour responses. In light of these disclosures, the skilled person would interpret feature A in a way which excluded type I IFN induced tumour cell apoptosis via activation of RIG-I by the claimed oligonucleotides.

4.7 These arguments do not convince the board. Claim 1 does not impose any limitation on the time between the binding of the claimed oligonucleotides to RIG-I and induction of tumour cell apoptosis. Hence, from reading claim 1 on its own, the skilled person would not exclude the appellant-opponent's interpretation of feature A.

4.8 The same conclusion applies when reading claim 1 in light of the description of the patent.

4.8.1 The board acknowledges that the paragraphs of the patent cited by the appellant-patent proprietor distinguish between the following two anti-tumour effects of the claimed oligonucleotides:

(a) induction of type I IFN production (in tumour cells)

(b) induction of apoptosis of tumour cells

4.8.2 As a consequence, the board accepts that the skilled person would understand the term "apoptosis of tumor cells" in these paragraphs to be a type I IFN independent anti-tumour effect. Such an interpretation is corroborated by Example 12 of the patent. This example comprises two experiments. The first (see paragraph [0336]) investigates tumour cell apoptosis already 24 hours after transfection of triphosphorylated 3p-2.2 siRNA (i.e. RIG-I ligand), non-triphosphorylated OH-2.2 siRNA and another control siRNA. By contrast, type I IFN induced tumour cell apoptosis occurs only after 48 hours of treatment (see reference to document D12 in point 4.6 above). The second experiment (see paragraph [0338]) is confined to assessing the apoptotic activity of 3p-2.2 siRNA in cells of a tumour model genetically engineered to suppress interferon-inducing activities.

4.8.3 However, it should not be overlooked that the passages of the patent cited by the appellant-patent proprietor disclose type I IFN induction as a further type of anti-tumour response of the claimed oligonucleotides. As explained in point 4.4 above, it was common general

knowledge at the effective date of the patent that type I IFN can induce tumour cell apoptosis. Absent any convincing argument by the appellant-patent proprietor why the skilled person would nonetheless understand the anti-tumour responses referred to in the aforementioned passages of the patent to exclude type I IFN dependent tumour cell apoptosis, the appellant-patent proprietor's arguments must fail.

4.9 To summarise, the board construes feature A in line with the appellant-opponent's interpretation of this feature. Hence, the use of claim 1 encompasses:

(a) direct induction of apoptosis of tumour cells through binding to RIG-I not involving binding of the claimed oligonucleotides to RIG-I and subsequent induction of type I IFN production

(b) induction of apoptosis of tumour cells through binding to RIG-I and subsequent induction of type I IFN production (in agreement with the appellant-opponent's interpretation of feature A)

5. Novelty - Article 100(a) EPC in conjunction with Article 54 EPC

5.1 The appellant-opponent argued lack of novelty of claim 1 over documents D1, D2, D4, D6b and D19.

5.2 For the reasons set out below (see points 6.11 and 6.12), the board is satisfied that the claimed subject-matter is novel vis-à-vis document D1. In view of the outcome of the appeal proceedings, the appellant-opponent's further objections of lack of novelty need not be discussed.

6. Inventive step - Article 100(a) EPC in conjunction with Article 56 EPC

6.1 The board's assessment of inventive step set out below concerns the subject-matter of claim 1 directed to the anti-tumour treatment referred to in point 4.9(b) above, i.e. induction of tumour cell apoptosis through binding of the claimed oligonucleotides to RIG-I and subsequent induction of type I IFN production.

The closest prior art

6.2 The appellant-opponent identified, *inter alia*, document D1 as the closest prior art. The appellant-patent proprietor disagreed with this choice. In its view, document D25 constituted the closest prior art.

6.3 A promising starting point is typically a prior-art document that relates to the claimed invention, in the sense that it discloses subject-matter conceived for the same purpose or aiming at the same objective, corresponding to a similar use, or relating to the same or a similar technical problem, or at least to the same or a closely related technical field. As a further criterion, the closest prior art should disclose subject-matter having the greatest number of relevant technical features in common with the claimed invention.

6.4 However, this does not mean that another prior-art document can be immediately ruled out as a possibly suitable starting point merely because it has a different purpose from the invention or fewer technical features in common with the invention than other, seemingly "closer" prior art (see Case Law of the Boards of Appeal of the European Patent Office, 10th

edn. 2022, I.D.3.1). In fact, a claimed subject-matter can only be considered inventive if it is not obvious starting from any piece of prior art.

6.5 In the case at issue, the board maintains its preliminary opinion set out in its communication that both documents D1 and D25 are suitable starting points.

6.6 Document D1 (see title, paragraphs [0012], [0014], [0063] to [0066], [0077]) discloses double-stranded and single-stranded RNA molecules of 21 to 29 nucleotides in length with 5'-triphosphates for inducing type I interferon in a cell to provide anti-viral and anti-cancer effects.

6.7 Hence, the RNA molecules ("5'-TP RNA") of document D1 exhibit the structural features defined in claim 1 and, like the claimed oligonucleotides, are capable of inducing type I IFN production and eliciting anti-cancer effects. As a consequence, the board is satisfied that document D1 represents a suitable starting point for the assessment of inventive step of claim 1.

6.8 The appellant-patent proprietor's arguments to the contrary are not found convincing.

6.8.1 Undeniably, the focus of document D1 is on antiviral effects, and tumour cell apoptosis is not mentioned. Moreover, document D1 does not support the anti-cancer effects it mentions with any experimental data. However, these facts do not render the 5'-TP RNA of document D1 unsuitable as a starting point for the assessment of inventive step of the claimed medical treatment, i.e. the treatment of a tumour in a vertebrate animal.

6.8.2 Likewise, the fact that document D1 does not mention RIG-I and furthermore proposes in paragraph [0061] a different mechanism of action of the 5'-TP RNA (i.e. activation of the Toll-like receptor 3) does not disqualify document D1 as a suitable starting point. The ability of the oligonucleotides to act as RIG-I ligands and to induce type I IFN production via binding to this receptor is implicit in view of common general knowledge (see points 3.2 and 3.3 above). Paragraph [0061], in turn, is confined to antiviral effects conferred by the 5'-TP RNA of document D1 in virus-infected cells, as argued by the appellant-patent proprietor itself.

6.8.3 The appellant-patent proprietor further argued that document D1 taught away from the claimed invention in that it disclosed in paragraphs [0081] and [0112] and in Table 3 that the 5'-TP RNA did not induce cell apoptosis. However, this argument is not convincing either since the passages relied on by the appellant-patent proprietor relate to experiments performed with virus-infected cells. Experimental results obtained in such cells are not transposable to tumour cells, as argued by the appellant-patent proprietor itself in the oral proceedings.

Distinguishing features vis-à-vis document D1

6.9 As outlined in points 6.6 and 6.7 above, document D1 discloses oligonucleotides exhibiting the structural features defined in claim 1 for inducing type I IFN in a cell to provide, *inter alia*, anti-cancer effects. The ability of these oligonucleotides to bind to RIG-I is implicit in view of the common general knowledge (see point 6.8.2 above).

6.10 As regards the claimed treatment of a tumour in a vertebrate animal, the appellant-patent proprietor did not dispute that the disclosure of the anti-cancer treatment in document D1 was enabling. The board does not doubt this either. As a consequence, the subject-matter of claim 1 does not differ from document D1 in this respect either.

6.11 By contrast, document D1 does not further specify the anti-cancer effects it reports on and hence fails to disclose that the induction of type I IFN by the 5'-TP RNA gives rise to apoptosis of tumour cells. This feature is not implicit either. As convincingly argued by the appellant-patent proprietor in the oral proceedings, it was common general knowledge at the effective date of the patent that type I IFN-mediated anti-tumour effects include effects which do not involve tumour cell apoptosis (see point 4.5 above). As a consequence, a skilled reader would not necessarily and unequivocally gather from the overall context of document D1 that the anti-cancer effects reported in it are tumour cell apoptotic effects.

6.12 It follows that the subject-matter of claim 1 differs from document D1 in that the type I IFN-mediated anti-tumour effect is induction of apoptosis of tumour cells.

Objective technical problem and solution

6.13 To formulate the objective technical problem effectively solved by the claimed subject-matter, the technical effect(s) associated with the distinguishing feature must be identified.

6.14 Relying on Examples 11 and 12 of the patent, the appellant-patent proprietor submitted that the claimed oligonucleotides achieved an improved anti-tumour response in vertebrate animals in that they provided in addition to an indirect, type I IFN-dependent induction of tumour cell apoptosis a direct, type I IFN-independent induction of tumour cell apoptosis.

6.15 However, the improvement invoked by the appellant-patent proprietor does not originate from the distinguishing feature defined in point 6.12 above alone since it is based in part on a type I IFN-independent tumour cell apoptotic effect. As a consequence, the alleged improvement cannot be taken into account for the formulation of the objective technical problem posed.

6.16 In the absence of any data demonstrating a technical effect linked to the distinguishing feature vis-à-vis the closest prior art, the objective technical problem to be solved is the provision of a further anti-tumour treatment with oligonucleotides in accordance with claim 1.

6.17 As a solution to this problem, the claimed invention proposes type I IFN induced apoptosis of tumour cells.

Assessment of obviousness

6.18 In the board's judgement, the proposed solution would have been obvious in light of document D12. The reasons are as follows.

6.19 Document D12 is a review article on the role of interferon-stimulated genes ("ISG") as mediators of apoptosis (see title). Document D12 can be considered

common general knowledge. It focuses primarily on cytotoxic/apoptotic effects of type I interferons on tumour cells and ISGs involved in the death process (see page 238, sentence bridging the left-hand and the right-hand columns). Hence, like document D1, document D12 describes anti-tumour effects of type I IFN. The skilled person thus would have had good reasons to consult document D12 with a view to solving the technical problem posed, i.e. the provision of a further anti-tumour treatment for oligonucleotides in accordance with claim 1.

6.20 From document D12 (see page 239, right-hand column, first and second full paragraphs), the skilled person would have learned that type I interferons induce apoptosis in various cancer types *in vitro* as well as *in vivo*. In view of this teaching, the skilled person would have been motivated to provide type I IFN induced apoptosis of tumour cells as a solution to the problem posed.

6.21 The board acknowledges that document D12 proposes, in addition to tumour cell apoptosis, various other, apoptosis-unrelated mechanisms of action for interferons' anti-tumour action (see Table 2). Nevertheless, the focus of document D12 is clearly on apoptotic effects of type I interferons on tumour cells (see point 6.19 above).

6.22 As regards the fact that document D12 qualifies the induction of apoptosis as a "possible" mechanism by which type I interferons exert their anti-tumour activity (see title of Table 2), in accordance with the case law of the boards, obviousness is not only at hand when the results are clearly predictable but also when there is a reasonable expectation of success (see Case

Law of the Boards of Appeal of the European Patent Office, 10th edn. 2022, I.D.7.1). In the case in hand, document D12's disclosure of type I IFN induced tumour cell apoptosis is based on experimental results observed in various *in vitro* and *in vivo* studies (see point 6.20 above).

6.23 Hence, there can be no doubt that the skilled person would have followed the teaching of document D12 with a reasonable expectation of solving the problem posed and would thus have arrived at the claimed subject-matter.

Overall conclusion on inventive step of the main request

6.24 The board concludes that the appellant's objection of lack of inventive step under Article 100(a) EPC in conjunction with Article 56 EPC prejudices the maintenance of the patent as granted.

Auxiliary requests 1 and 2

7. Claim 1 of each of auxiliary requests 1 and 2 is identical to claim 1 of the main request. Hence, the considerations set out above regarding inventive step of claim 1 of the main request equally apply to claim 1 of each of these two auxiliary requests.

Auxiliary request 3

8. Amendments - Article 123(2) EPC

8.1 The subject-matter of a European patent must not extend beyond the content of the application as filed. In accordance with established case law of the boards, the relevant question to be decided is whether the skilled person would have derived the subject-matter of the

patent directly and unambiguously from the application as filed, meaning that the subject-matter must not contain technical information which a skilled person would not have objectively derived from the application as filed.

8.2 Turning to the current case, claim 1 of auxiliary request 3 stipulates, *inter alia*, that the claimed oligonucleotide directly induces apoptosis of tumour cells through binding to RIG-I.

8.3 Hence, claim 1 of auxiliary request 3 differs from claim 1 of the main request solely in that the induction of apoptosis of tumour cells must be direct.

8.4 The appellant-opponent did not specifically address the amendment made to claim 1 of auxiliary request 3 but argued in the context of claim 1 of the main request (see point XV. above) that the application as filed lacked direct and unambiguous disclosure of the claimed oligonucleotide for use in inducing apoptosis of tumor cells through binding to RIG-I.

No preference in the application as filed for the claimed oligonucleotides over bacterial RNA

8.5 As correctly argued by the appellant-opponent (statement of grounds, point 1.3), the application as filed discloses oligonucleotides and bacterial RNA as separate, equivalent embodiments for inducing anti-tumor responses comprising type-I IFN induction and/or tumor cell apoptosis (see page 59, lines 7 to 8 and 21 to 31 of the application as filed).

8.6 The appellant-patent proprietor took a different view, arguing that the skilled reader would understand the

oligonucleotide disclosed on page 63, lines 8 to 13 of the application as filed, to be preferred over bacterial RNA in light of the following disclosures:

(a) the claims as originally filed, focusing on oligonucleotides

(b) the summary of the invention (page 5, lines 1 to 11 of the application as filed) which solely referred to oligonucleotides or precursors thereof, not to bacterial RNA

(c) Examples 1 to 7 of the application as filed, using oligonucleotides for identifying the binding motif specifically recognised by RIG-I

(d) Examples 12, 13 and 15 of the application as filed, demonstrating that an oligonucleotide binding and activating RIG-I is capable of inducing type I IFN production and inducing apoptosis through binding to RIG-I

8.7 The board does not concur.

8.7.1 Even if most of the claims as originally filed relate to oligonucleotides and precursors thereof, it remains that independent claim 31 is directed to bacterial RNA for preventing and/or treating various disorders, including tumor, in a vertebrate animal. As a consequence, the claims as originally filed do not point to a preference for oligonucleotides disclosed on page 63, lines 8 to 13 of the application as filed over bacterial RNA.

8.7.2 The same holds true for the single passage on page 5, lines 1 to 11 of the application as filed. It is

immediately evident from the passages of the application as filed cited by the appellant-opponent (see point 8.5 above) that the invention disclosed therein pertains not only to oligonucleotides and precursors thereof but also to bacterial RNA.

8.7.3 What is more, the application as filed discloses all of these three actives as RIG-I ligands (see page 63, lines 15 to 17 immediately following the passage on page 63, lines 8 to 13 and referring to the same embodiment) and pertains in one of its examples to bacterial RNA (see example 10).

8.7.4 Concerning Examples 12, 13 and 15 of the application as filed, the board accepts that these show, *inter alia*, direct, IFN-independent anti-tumor effects of the RIG-I ligand 3p-2.2 siRNA amongst which early, type-I IFN independent tumor cell apoptosis. The same applies for Figure 16 and Example 16 of the application as filed, referred to by the appellant-patent proprietor in the oral proceedings. The board agrees, however, with the appellant-opponent in finding that none of these passages directly and unambiguously disclose that this effect occurs through binding of 3p-2.2 siRNA to RIG-I (point 1.3.2 of the appellant-opponent's statement setting out the grounds of appeal). Notably, Example 12 (see heading of this example and page 98, line 24) shows that the early tumor cell apoptosis observed therein does not involve Cardif, i.e. an adaptor protein in the RIG-I signaling pathway (see point 3.2 above). As a consequence, the examples relied on by the appellant-patent proprietor do not provide adequate support for the alleged preference of oligonucleotides disclosed on page 63, lines 8 to 13 of the application as filed over bacterial RNA either.

8.8 It follows that the application as filed discloses the claimed oligonucleotides and bacterial RNA as two equal alternatives.

Direct induction of apoptosis of tumor cells through binding of the claimed oligonucleotide to RIG-I

8.9 Among the passages indicated by the appellant-patent proprietor as basis for the subject-matter of claim 1 (see point XIV. above), only the passage on page 63, lines 8 to 13 of the application as filed discloses a causal link between binding of an oligonucleotide in accordance with claim 1 to RIG-I, on the one hand, and induction of tumour cell apoptosis, on the other hand.

This passage reads as follows:

"In one embodiment, the pharmaceutical composition is a tumor vaccine. The oligonucleotide or precursor thereof described in the invention or the bacterial RNA may induce tumor cell apoptosis through binding to RIG-I, induce type I IFN, IL-18 and/or IL-1β production by the tumor cells, directly and/or indirectly activate effector cells of innate immunity such as NK cells, NKT cells, and γδ T cells, and/or directly and/or indirectly inactivate suppressor T cells, thereby leading to tumor cell growth inhibition and/or destruction."

8.10 As correctly observed by the appellant-opponent (statement of grounds of appeal, point 1.2.2), this passage comprises two lists, namely:

(a) a first list of active agents, i.e. "[t]he oligonucleotide or precursor thereof described in the invention or the bacterial RNA"

(b) a second list citing various anti-tumour effects, occurring alone or in combination, including induction of tumour cell apoptosis through binding to RIG-I

8.11 To the appellant-patent proprietor's advantage, the board will assume that it is implicit from the context of the passage on page 63, lines 8 to 13 of the application as filed that the induction of tumour cell apoptosis through binding to RIG-I disclosed in this passage is a direct, IFN-independent apoptotic effect.

8.12 Moreover, it is assumed that the "oligonucleotide [...] described in the invention" mentioned on page 63, lines 8 to 9 of the application as filed is an oligonucleotide in accordance with page 36, lines 20 to 28 of the application as filed.

8.13 It remains, however, that a selection out of the aforementioned two lists must be performed to arrive at an oligonucleotide in accordance with page 36, lines 20 to 28 of the application as filed for use in directly inducing apoptosis of tumour cells through binding to RIG-I.

8.14 In accordance with the boards' established case law, the content of the application as filed must not be seen as a reservoir of features from which features pertaining to separate embodiments can be combined to artificially create a particular embodiment. A combination of features originally disclosed separately or selected from several lists may be directly and unambiguously derivable from the application as filed, provided the application as filed contains explicit or implicit pointers to the specific combination.

8.15 In the case at issue, the board is unable to identify any pointer in the application as filed towards oligonucleotides as claimed for the purpose of directly inducing tumour cell apoptosis through binding to RIG-I.

8.16 The appellant-patent proprietor referred to the disclosures on page 23, lines 16 to 19 and page 59, lines 7 to 31 of the application as filed as pointers to the claimed anti-tumour effect of directly inducing tumour cell apoptosis through binding to RIG-I.

8.17 However, these two passages fail to mention RIG-I. Furthermore, these passages refer not only to type I IFN independent induction of tumour cell apoptosis but also to type I IFN-mediated anti-tumour responses. As explained in point 4.5 above, the latter include anti-tumour effects unrelated to apoptosis of tumour cells.

8.18 Likewise, Example 16 of the application as filed reports anti-tumour effects of 3p-2.2 siRNA which do not involve induction of tumour cell apoptosis.

8.19 As a consequence, the appellant-patent proprietor's argument must fail.

8.20 It follows that absent any pointer in the application as filed towards oligonucleotides as claimed for the purpose of inducing tumour cell apoptosis through binding to RIG-I, the subject-matter of claim 1 is not directly and unambiguously derivable from the application as filed, contrary to the requirements of Article 123(2) EPC.

Appellant-patent proprietor's further arguments

8.21 In the oral proceedings, the appellant-patent proprietor recalled that the strict "photographic standard" developed by the boards did not apply anymore, as evidenced by decision T 1621/16, discussing amendments based on multiple selections from lists of converging alternatives. The legal purpose of Article 123(2) EPC was to prevent a patent proprietor from getting an unwarranted advantage by obtaining patent protection for subject-matter which had not been invented at the effective date of the patent. In the case in hand, the claimed invention did not give rise to such an unwarranted advantage, as evidenced by the fact that the board had found the claimed invention to be novel, inventive and sufficiently disclosed.

8.22 These arguments are not convincing.

8.22.1 Under established case law of the boards, the gold standard for assessing whether the subject-matter of a patent extends beyond the content of the application as originally filed is whether the amendment of the claims results in subject-matter which is directly and unambiguously derivable by a skilled person, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the documents as filed (see e.g. decision of the Enlarged Board of Appeal G 2/10, point 4.3 of the Reasons). Contrary to the case underlying decision T 1621/16, the amendments in dispute are not a combination of converging alternatives nor is the claimed combination supported by a pointer in the application as filed.

8.22.2 Hence, in the current case, the subject-matter of claim 1 is not directly and unambiguously derivable from the application as filed for the reasons set out above.

Auxiliary requests 4 to 15

9. Amendments - Article 123(2) EPC

9.1 At the oral proceedings, the board informed the appellant-patent proprietor of its preliminary opinion that the objection of added subject-matter against claim 1 of auxiliary request 3 seemed to apply to claim 1 of all the remaining auxiliary requests on file, since they also comprised combinations of features involving selection from lists.

9.2 In response, the appellant-patent proprietor did not submit any further arguments or comments on auxiliary requests 4 to 15.

9.3 The board therefore concludes that claim 1 of each of auxiliary requests 4 to 15 does not comply with the requirements of Article 123(2) EPC either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

M. Schalow T. Sommerfeld

Decision electronically authenticated