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Datasheet for the decision of 20 October 2016

Case Number: T 0814/12 - 3.3.04

Application Number: 03790894.4

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Language of the proceedings: EN

Title of invention:
Use of protein kinase N beta

Patent Proprietor:
Silence Therapeutics GmbH

Opponent:
Alnylam Pharmaceuticals Inc.

Headword:
Target in PI3-kinase pathway/SILENCE THERAPEUTICS

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2), 123(3)
EPC R. 115(2)
RPBA Art. 13(1), 15(3)

Keyword:

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T 0241/95

Catchword:

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Case Number: T 0814/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 20 October 2016

Appellant: (Patent Proprietor)	Silence Therapeutics GmbH Robert-Rössle-Strasse 10 13125 Berlin (DE)
Representative:	Stratagem IPM Limited Meridian Court Comberton Road Toft, Cambridge CB23 2RY (GB)
Appellant: (Opponent)	Alnylam Pharmaceuticals Inc. 300 Third street, Third Floor Cambridge MA 02142 (US)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 February 2012 concerning maintenance of the European Patent No. 1536827 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	M. Montrone
	L. Bühler

Summary of Facts and Submissions

I. Appeals were lodged by the patent proprietor (hereinafter "appellant I") and the opponent (hereinafter "appellant II") against the interlocutory decision of the opposition division concerning European patent No. 1 536 827. The patent is based on European patent application No. 03 790 894.4 which was filed as an international application and published as WO 2004/019973 (hereinafter "the application as filed") with the title "*Use of protein kinase N beta*".

II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC), and under Articles 100(b) and 100(c) EPC.

III. In the impugned decision the opposition division held that the patent did not disclose the subject-matter of claims 4, 6, 8 and 10 of the main request and of auxiliary requests 1 and 2 in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. With regard to auxiliary requests 3 and 4, it took the view that the subject-matter of claims 13, 17, 19, 20 and 22 lacked an inventive step, while the claims of auxiliary request 5 were held to meet the requirements of the EPC.

IV. With its statement of grounds of appeal appellant I submitted a new main and five auxiliary requests. Subsequently, two further auxiliary requests were submitted.

V. With its statement of grounds of appeal appellant II submitted arguments why the opposition division had erred in the impugned decision to find that the

subject-matter of claims 1 and 2 of auxiliary request 5 was novel over the disclosure of document D2. Appellant II further submitted that the subject-matter of claims 1 to 27 of auxiliary request 5 lacked an inventive step in view of the combined teachings of documents D1 and D15 or in the light of the teaching of document D2 either alone or in combination with that of document D1 (the documents are identified in section IX below). Moreover, appellant II submitted that the patent did not disclose the subject-matter of claims 3 and 5 of auxiliary request 5 in a manner that it could be carried out by a person skilled in the art.

VI. Appellants I and II each replied to the other party's statement of grounds of appeal.

VII. The board summoned the parties to oral proceedings. Subsequently, appellant II announced that it would not be attending the oral proceedings.

VIII. Oral proceedings before the board were held on 20 October 2016. During the oral proceedings, appellant I filed a new main request and withdrew all the other pending claim requests. At the end of the oral proceedings the chairwoman announced the board's decision.

Independent claims 1, 3, 11 to 16 and 20 of the main request read:

"1. Use of protein kinase N beta or a fragment thereof, whereby such fragment realises the effects of protein kinase N beta, for the manufacture of a diagnostic agent for the diagnosis of a disease, whereby the disease is selected from the group consisting of metastatic cancers and any pathological conditions

involving the PI 3-kinase pathway, whereby such pathological condition is preferably selected from the group consisting of endometrial cancer, gliomas, endometrial hyperplasias, Cowden's syndrome, hereditary non-polyposis colorectal carcinoma, Li-Fraumene's syndrome, breast-ovarian cancer; prostate cancer, BannayanZonana syndrome, LDD (Lhermitte-Duklos' syndrome), hamartoma-macrocephaly diseases including Cow disease (CD) and Bannayan-Ruvalcaba-Rily syndrome (BRR), mucocutaneous lesions such as trichilemmonmas, macrocephaly, mental retardation, gastrointestinal harmatomas, lipomas, thryroid adenomas, fibrocystic disease of the breast, cerebellar dysplastic gangliocytoma, breast and thyroid malignancies and large cell carcinoma, small cell carcinoma and squamous cell carcinoma."

Claim 3 differs from claim 1 in that the feature "Use of protein kinase N beta" is replaced by the feature "Use of a nucleic acid coding for protein kinase N beta".

"11. Use of an antibody against protein kinase N beta or a part thereof which antibody interacts with protein kinase N beta or a part thereof, for the manufacture of a medicament for the treatment and/or prevention of a disease, whereby the disease is selected from metastatic cancers."

Claim 12 differs from claim 1 in that the feature "Use of protein kinase N beta or a fragment thereof, whereby such fragment realises the effects of protein kinase N beta" is replaced by the feature "Use of an antibody against protein kinase N beta or a part thereof which antibody interacts with protein kinase N beta or a part thereof".

Claim 13 differs from claim 11 in that the feature "Use of an antibody against protein kinase N beta or a part thereof which antibody interacts with protein kinase N beta or a part thereof" is replaced by the feature "Use of a nucleic acid which interacts with protein kinase N beta or a part thereof" and wherein the feature "whereby the nucleic acid is selected from the group which comprises aptamers and spiegelmers" is added at the end.

Claim 14 differs from claim 1 in that the feature "Use of protein kinase N beta or a fragment thereof, whereby such fragment realises the effects of protein kinase N beta" is replaced by the feature "Use of a nucleic acid which interacts with protein kinase N beta or a part thereof".

Claim 15 differs from claim 11 in that the feature "Use of an antibody against protein kinase N beta or a part thereof which antibody interacts with protein kinase N beta or a part thereof" is replaced by the feature "Use of a nucleic acid which interacts with a nucleic acid coding for protein kinase N beta or a part thereof" and wherein the feature "whereby the interacting nucleic acid is an antisense oligonucleotide, a ribozyme and/or siRNA" is added at the end.

Claim 16 differs from claim 1 in that the feature "Use of protein kinase N beta or a fragment thereof, whereby such fragment realises the effects of protein kinase N beta" is replaced by the feature "Use of a nucleic acid which interacts with a nucleic acid coding for protein kinase N beta or a part thereof" and wherein the feature "whereby the interacting nucleic acid is an

antisense oligonucleotide, a ribozyme and/or siRNA" is added at the end.

"20. Use of a kit for in vitro characterisation of a disease or a condition which is selected from metastatic cancers, whereby such kit comprises at least one agent which is selected from the group comprising protein kinase N beta or a part thereof, whereby such part realises the effects of protein kinase N beta, antibodies specific for protein kinase N beta or a part thereof, whereby such part realises the effects of protein kinase N beta, polypeptides interacting with protein kinase N beta or a part thereof, whereby such part realises the effects of protein kinase N beta, polypeptides interacting with a nucleic acid coding for protein kinase N beta or a part thereof, whereby such part realises the effects of protein kinase N beta, nucleic acids interacting with protein kinase N beta or a part thereof, whereby such part realises the effects of protein kinase N beta, nucleic acids interacting with a nucleic acid coding for protein kinase N beta or a part thereof, whereby such part of protein kinase N beta realises the effects of protein kinase N beta, and optionally at least one other compound."

IX. The following documents are cited in this decision:

D1: Oishi K. *et al.*, Biochem. and Biophys. Research Comm., 261, 808-814, 1999

D2: WO 00/73469

D3: Alexander K. *et al.*, Thiemes Innere Medizin, 601-604, 1999

D8: WO 91/19813

D9: WO 98/08856

D15: Jiménez C. *et al.*, J. Cell Biol., 151, 249-261, 2000

D17: Vazquez F. *et al.*, Biochim. Biophys. Acta, 1470, M21-M35, 2000

D19: Di Cristofano A. *et al.*, Nat Genet., 19(4), 348-355, 1998

D20: Eng, C. *et al.*, Human Mutation, 22, 183-198, 2003

D22: Stein R. C. and Waterfield M. D., Molecular Medicine Today, 6, 347-357, 2000

D23: Roymans D. and Siegers H., Eur. J. Biochem., 268, 487-498, 2000

X. Appellant I's arguments may be summarised as follows:

Main request

Extension of protection (Article 123(3) EPC)

The extent of protection conferred by the subject-matter of claims 1, 3, 12, 14, and 16 was restricted compared to that of the corresponding claims 3, 5, 18, 21, 23 as granted. This was so because the replacement of the term "*comprising*" by "*consisting*" in the wording "*whereby the disease is selected from the group comprising metastatic cancer and any pathological conditions involving the PI3-kinase pathway*" in the claims as granted limited the diagnostic applications to metastatic cancer and pathological conditions

involving the PI3-kinase pathway. This limitation was effective irrespective of the second amendment whereby the term "*consists of*" in the wording "*whereby such pathological condition consists of*" of the claims as granted was replaced by "*is preferably selected from the group consisting of*".

Clarity and support (Article 84 EPC)

The feature "*any pathological conditions involving the PI3-kinase pathway*" cited in claims 1, 3, 12, 14 and 16 had been present in the claims as granted and was thus not contestable pursuant to Article 84 EPC (see decision G 3/14).

Sufficiency of disclosure (Article 83 EPC)

The subject-matter of claims 1 and 3 was directed to either the use of protein kinase N beta (PKNbeta), or a nucleic acid encoding it, for the manufacture of a diagnostic agent. Diagnostic assays based on these two agents were not disclosed in the patent. However, this was immaterial with regard to sufficiency of disclosure because the skilled person, relying on his common general knowledge, knew that using labelled PKNbeta in a standard competition assay allowed the claimed subject-matter to be put into practice without undue burden.

The patent disclosed that the gene expression of PKNbeta was increased in a PI3-kinase-dependent manner in metastatic tumour cells (examples 3 and 12), which demonstrated that PKNbeta was a downstream member of the PI3-kinase pathway. This result further demonstrated that the increased PKNbeta gene expression was a suitable diagnostic marker for metastatic

tumours. Furthermore, since it was known from the prior art that all of the diseases cited in claims 1, 3, 12, 14 and 16 were associated with a permanently activated PI3-kinase pathway (documents D16, D17, D19, D20, D22 and D23), the PI3-kinase-mediated increased gene expression of PKNbeta demonstrated the suitability of PKNbeta as a diagnostic marker for all pathological conditions involving the PI3-kinase pathway.

Although document D1 reported that PKNbeta was not over-expressed in all of the tumour cell lines tested (Figure 10), this did not cast doubt on PKNbeta's suitability as a diagnostic marker in metastatic tumours. This was so because, firstly, tumours were not necessarily all metastatic but could also be non-metastatic, and secondly, document D1 did not disclose that the tumour cell lines tested were metastatic. Moreover, in opposition-appeal proceedings the burden of proof lied with the opponent, i.e. appellant II.

As regards the therapeutic applications referred to in claim 11, 13 and 15, examples 4 to 8 of the patent disclosed that agents, which selectively inhibited PKNbeta gene expression, also prevented the spreading of tumour cells and their growth. This demonstrated the suitability of these agents in the therapy of metastatic cancer, since cell spreading was a characteristic of metastasis (document D15, page 249, column 1, second paragraph).

Inventive step (Article 56 EPC)

The disclosure of either of documents D1 or D2 represented the closest prior art for the subject-matter of independent claims 1, 3, 11 to 16 and 20.

Document D1 disclosed that PKNbeta was over-expressed in a subset of cancer cell lines. The document did not disclose that the cell lines tested were metastatic, nor did it disclose therapeutic or diagnostic approaches involving PKNbeta or agents directed against PKNbeta.

Document D2 disclosed 123 different kinases, including PKNbeta (SEQ ID NO: 133). However, the document reported no experimental data revealing the function of PKNbeta, except that its gene was expressed (example 4). Furthermore, document D2 disclosed twelve diseases which might be associated with the 123 kinases, including, *inter alia*, cancer (page 63, lines 22 to 25). However, this did not provide - and the document did not disclose anything more in this respect - any guidance on whether the kinases qualified as a marker or target in the diagnosis or therapy of the 12 specific diseases cited. Accordingly, the disclosure of document D2 was an invitation to the skilled person in assessing the potential involvement of the kinases, for example PKNbeta, in the diseases cited and to conduct further research; it was thus not enabling.

The subject-matter of claims 1, 3, 11 to 16 and 20 differed from the disclosure in either of documents D1 or D2 by indicating the disease to be treated or diagnosed.

The technical problem was the provision of means for the use in the diagnosis or treatment of the disorders referred to in the claims.

With regard to obviousness, neither of the teachings of documents D1 or D2 suggested that PKNbeta was a part of the PI3-kinase signalling pathway and was thus over-

expressed in metastatic cancer or in diseases involving the PI3-kinase pathway.

Although document D1 disclosed that PKNbeta was over-expressed in certain tumour cell lines, this was not a hint to PKNbeta's usefulness in the diagnosis or treatment of metastatic cancer. This was so since tumour cell lines had not necessarily to be metastatic and document D1 did not disclose that the tested cell lines were metastatic. Further, metastasis was the result of the expression of particular genes causing complex cellular re-organisations (documents D15, page 249, column 1, "Introduction", first paragraph; D3, Figure 3.79) and there were no hints derivable from the prior art that PKNbeta was potentially involved therein.

Document D1 reported further that PKNbeta bound to active RhoA. It speculated that PKNbeta might therefore be involved in RhoA signalling pathways. However, this provided no hint that PKNbeta was a member of the PI3-kinase pathway. This was also not derivable from the teaching of document D1 when combined with that of document D15. Document D15 reported that RhoA was inhibited by the regulatory subunit of PI3-kinase. However, no conclusions could be drawn about a potential influence of PI3-kinase on PKNbeta from this disclosure either. Moreover, the teachings of documents D1 and D15 with regard to the binding of PKNbeta to RhoA were even contradictory, since the former disclosed that PKNbeta bound to activated RhoA, while the latter reported that PI3-kinase inhibited the activity of RhoA.

XI. Appellant II's written arguments may be summarised as follows:

Main request

Extension of protection (Article 123(3) EPC)

The scope of protection conferred by the subject-matter of claims 1, 3, 12, 14, and 16 was extended compared to their corresponding claims 3, 5, 18, 21, 23 as granted. Although the first replacement of "comprising" by "consisting" in the claims as granted was a limitation, the second amendment regarding the replacement of "consists of" by "is preferably selected from the group consisting of" extended the protection conferred. This was so because the diseases encompassed by the amended claims comprised diseases involving the PI3-kinase pathway which were no longer restricted to the ones cited, contrary to the claims as granted.

Clarity and support (Article 84 EPC)

Owing to the term "preferably", the amended feature "pathological conditions involving the PI 3-kinase pathway, whereby such pathological condition is preferably selected from the group consisting of" referred to in claims 1, 3, 12, 14, and 16, related not only to the specifically cited diseases but also extended to additional diseases which were functionally defined in terms of a molecular mechanism, i.e. by their involvement in the PI3-kinase pathway. This latter definition was unclear (see decision T 241/95).

Sufficiency of disclosure (Article 83 EPC)

The methods according to claims 1 and 3 could be carried out by the skilled person only when PKNbeta was labelled and used in a competition assay. Such an assay was however not disclosed in the patent. In the absence of any guidance in the patent on how to perform the claimed diagnostic methods, the skilled person would not have considered using labelled PKNbeta in a competition assay in order to perform the claimed diagnostic applications. Even assuming that the skilled person took a competition assay into consideration, the subject-matter of claims 1 and 3 could not have been carried out across the whole ambit of the claims because they were not restricted to such an assay.

Inventive step (Article 56 EPC)

Either of documents D1 or D2 represented the closest prior art for the subject-matter of claims 1, 3, 11 to 16 and 20.

Document D1 disclosed that PKNbeta was over-expressed in specific human cancer cell lines, *inter alia,* in the colorectal adenocarcinoma cell line SW480 and in HeLa cells (page 811, Figure 3). Its over-expression suggested a particular role in immortalised cell lines which were established models of tumour diseases. Furthermore, document D1 disclosed that PKNbeta bound in an *in vitro* assay to the RhoA protein (page 811, first paragraph). Document D1, however disclosed no diagnostic assays based on PKNbeta over-expression or therapeutic agents directed against PKNbeta.

The subject-matter of claims 1, 3, 11 to 16 and 20 differed from the disclosure in document D1 in that it

related to the claimed diagnostic or therapeutic applications by means of PKNbeta or agents directed against it. The technical problem was thus the provision of means for diagnosis or therapy of disorders known to be PKNbeta-associated.

This problem was not solved by the subject-matter of claims 1, 3, 12, 14, 16 across the whole ambit of the claims. The patent disclosed in example 12 that activated PI3-kinase increased the gene expression of PKNbeta in two metastatic cancer cell lines. This was not enough to support the generic concept that PKNbeta was over-expressed in all metastatic tumours and thus a diagnostic marker in these diseases. Also document D1 did not support this concept, since it disclosed that PKNbeta was over-expressed in only three of the eight tested cancer cell lines.

Furthermore, the subject-matter of claims 11, 13 and 15 did not solve the problem across the whole ambit of the claims. The patent disclosed in examples 4 to 8 that inhibitors of PKNbeta gene expression reduced the growth of two metastatic cancer cell lines. PKNbeta was over-expressed in these two cell lines, which implied that the therapeutic effect of the inhibitors necessarily relied on PKNbeta's strong gene expression. Document D1, however, disclosed that PKNbeta was not over-expressed in all metastatic cancers.

The subject-matter of claims 1 and 3 was obvious in the light of the teaching of document D1 alone, which disclosed that PKNbeta was over-expressed in several cancer cell lines. It was also obvious in the light of the teaching of document D1 combined with that of document D15, since the former disclosed that PKNbeta bound to RhoA, which according to the latter was (i) a

member of the PI3-kinase pathway and (ii) functionally involved in cell migration, i.e. a characteristic of metastasis (document D15, Figure 10). In view of this, the subject-matter of claims 11 to 16 and 20 was obvious too, because once the use of PKNbeta as a diagnostic marker or therapeutic target in metastatic cancer or diseases involving the PI3-kinase pathway was obvious, then the screening for agents interacting with it, for example, antibodies or nucleic acids, was a matter of routine for the person skilled in the art.

Document D2 as an alternative closest prior art disclosed that PKNbeta was *inter alia* a novel tumour marker and could be used in the diagnosis of cancer (pages 62 and 63). Also anti-PKNbeta antibodies as diagnostic agents of *inter alia* cancer were disclosed in document D2 (page 52, lines 9 to 14 and page 53, line 6 to page 54, line 3 and page 54, lines 10 to 18).

The subject-matter of claims 1, 3, 11 to 16 and 20 differed from the disclosure in document D2 in that it referred to specific diagnostic or therapeutic applications. The technical problem was the provision of means for use in the diagnosis or therapy of pathological conditions associated with PKNbeta expression.

Document D1 disclosed that PKNbeta was over-expressed in several human tumour cell lines including adenocarcinomas, which metastasised (document D3). Thus, the use of PKNbeta in the diagnosis of metastatic cancers was obvious to the skilled person. Antibodies were generally used as therapeutic agents. It was therefore obvious to the skilled person that the diagnostic antibodies disclosed in document D2 were also suitable agents in the therapy of metastatic

cancers. Accordingly, claims 11 and 12 did not meet the requirements of Article 56 EPC. The same applied to the therapeutic or diagnostic use of aptamers, spiegelmers, antisense molecules, ribozymes or siRNA according to claims 13 to 16, since these molecules represented standard therapeutic or diagnostic alternatives to antibodies (documents D8 and D9).

XII. Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 20 of the main request filed during the oral proceedings of 20 October 2016.

Appellant II requested in writing that the decision under appeal be set aside and that European patent No. 1 536 827 be revoked.

Reasons for the Decision

1. The duly summoned appellant II was not present at the oral proceedings. In accordance with Rule 115(2) EPC and Article 15(3) RPBA the board decided that the proceedings be continued in its absence.

Admission of the new main request into the proceedings

2. The new main request was filed by appellant I during the oral proceedings. The submission of this request is therefore an amendment to appellant I's case and its admission is at the board's discretion (Article 13(1) RPBA).

3. The new main request addressed by way of deletion of either whole claims or single embodiments thereof

objections under Articles 54 and 56 EPC raised by appellant II in its statement of grounds of appeal (see points 1 to 1.6 and 2.2.2) and objections under Article 83 EPC raised in appellant II's reply (see point 7) to appellant I's statement of grounds of appeal. Given the structure of the claims, the amendments made were straightforward, did not raise new issues or increase the complexity of the appeal case. Consequently, the board decided to admit the request into the proceedings (Article 13(1) RPBA).

Main request

Amendments (Article 123(2) EPC)

4. Appellant II has not raised objections pursuant to Article 123(2) EPC against the former main request submitted by appellant I with its statement of grounds of appeal.

5. The present main request differs from the former one,

(i) in that former claims 1, 2, 13 to 17, 19 and 27 have been deleted,

(ii) in that the diseases "colorectal carcinomas" and "adenocarcinomas" have been deleted in present claims 1, 3, 12, 14 and 16, and

(iii) in that the features "and any pathological conditions involving the PI 3-kinase pathway, whereby such pathological condition is preferably selected from the group consisting of endometrial cancer, gliomas, endometrial hyperplasias, Cowden’s syndrome, hereditary non-polyposis colorectal carcinoma, Li-Fraumene’s

syndrome, breast-ovarian cancer; prostate cancer, BannayanZonana syndrome, LDD (Lhermitte-Duklos' syndrome), hamartoma-macrocephaly diseases including Cow disease (CD) and Bannayan-Ruvalcaba-Rily syndrome (BRR), mucocutaneous lesions such as trichilemmonmas, macrocephaly, mental retardation, gastrointestinal harmatomas, lipomas, thryroid adenomas, fibrocystic disease of the breast, cerebellar dysplastic gangliocytoma, breast and thyroid malignancies and large cell carcinoma, small cell carcinoma and squamous cell carcinoma" have been deleted from claims 11, 13 and 15.

Furthermore, the present main request differs in that

(iv) the feature "and any pathological conditions involving the PI 3-kinase pathway" has been deleted from claim 20, and in that

(v) the databank entries "PID g7019489 or databank entry gi 7019489, or a part thereof" have been deleted from present claims 2 and 4 and the entries "gi 7019488 or NM_01335, preferably NM_01335.1" have been deleted from present claims 5, 6 and 8.

Lastly, present claims 1, 3, 12, 14 and 16 have been amended

(vi) by replacing the term "comprising" with "consisting of" in the wording "preferably selected from the group comprising".

6. It is evident that, in the present case, the deletion of either complete claims or alternative embodiments in a claim (see items (i) to (v) in point 5 above) does not extend the subject-matter beyond the content of the

application as filed. Furthermore, there is a basis for the amended feature "preferably selected from the group consisting of" in claims 1, 3, 12, 14 and 16 on page 10, last paragraph of the application as filed.

7. Accordingly, the main request meets the requirements of Article 123(2) EPC.

Extension of protection (Article 123(3) EPC)

8. Article 123(3) EPC stipulates that the claims of a patent as granted may not be amended in such a way as to extend the protection it confers. It is established case law of the boards of appeal that in deciding whether or not this requirement is met, it is necessary to compare the protection conferred by the totality of the claims as granted with that of the amended claims (see Case Law of the Boards of Appeal of the EPO, 8th edition 2016 (hereinafter "CLBA"), II.E.2.2).

9. Independent claims 1, 3, 12, 14 and 16 of the main request differ from their corresponding claims 3, 5, 18, 21 and 23 as granted in that

(i) the diseases "colorectal carcinomas" and "adenocarcinomas" have been deleted, and

(ii) by the replacement of the term "comprising" with "consisting" in the wording "whereby the disease is selected from the group comprising metastatic cancer and any pathological conditions involving the PI3-kinase pathway" in the claims as granted.

Furthermore, they differ in that (iii) the term "consists of" in the wording "whereby such pathological

condition consists of" in the claims as granted has been replaced by "is preferably selected from the group consisting of".

10. It is evident that amendment (i) set out in point 9 above does not extend the protection conferred since two alternative embodiments have been deleted from the claims. Amendment (ii) limits the extent of protection conferred compared to the claims as granted - owing to the use of the term "consisting" instead of the term "comprising" - to the two diagnostic applications referred to in the claim, i.e. metastatic cancer and any pathological conditions involving the PI3-kinase pathway, thus excluding diagnostic applications to further unspecified diseases which were encompassed in the claims as granted because of the term "comprising".

11. Appellant II submitted that the protection conferred by claims 1, 3, 12, 14, and 16 was extended by the amendment (iii) set out in point 9 above because - unlike in the claims as granted - the feature "whereby such pathological condition is preferably selected from the group consisting of" (hereinafter the "amended feature") did not define the diseases to be diagnosed as only those specifically cited in the claims but extended the definition to further unspecified ones.

12. The board is not convinced by this argument. Although the amended feature lifts the restriction in the amended claims to the specific diseases cited, the protection conferred by the claims is not extended. This is so because the claims as granted also related to more than the specifically cited diseases (see point 10 above), which necessarily included any disease involving the PI3-kinase pathway.

13. The main request thus complies with the requirements of Article 123(3) EPC.

Clarity and support (Article 84 EPC),

14. Claims 1, 3, 12, 14, and 16 define the diseases to be diagnosed *inter alia* as "pathological conditions involving the PI3-kinase pathway, whereby such pathological condition is preferably selected from the group consisting of [...]".

15. Appellant II submitted that the amended feature, to the extent that it related to diseases that were defined only functionally in terms of a molecular mechanism, i.e. in that they were "pathological conditions involving the PI3-kinase pathway" lacked clarity in view of, e.g., decision T 241/95 of 14 June 2000.

16. The board is not convinced by appellant II's argument.

16.1 The functional definition of a disorder in a claim *per se* - in this case by its molecular mechanism - does not necessarily amount to a lack of clarity.

16.2 Decision T 241/95 itself, for example, describes the conditions to be fulfilled in order that a functional definition be allowable. Headnote II and point 3.1.1 of the Reasons read: "*the claim can be regarded as clear only if instructions, in the form of experimental tests or any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise which conditions fall within the functional definition and accordingly within the scope of the claim*" (emphasis added).

17. The patent and the cited prior art documents disclose that PI3-kinase, the pathway involving this enzyme, and disorders associated with this pathway are commonly known in the art at the priority date of the contested patent. These documents further report that a chronic *"hyperactivation*" or "*activation*" of the PI3-kinase is the major contributor to these disorders (see e.g. paragraphs [0035] and [0036] of the patent and e.g. document D23, abstract, page 489, column 1, second paragraph). This means that the skilled person for assessing whether or not a disease falls into the ambit of the claims has to determine the activity of the PI3-kinase. Documents D22 and D23, for example, disclose that the active enzyme catalyses the phosphorylation of inositol lipids at the D-3 position of the inositol ring, i.e. a modification which is readily determinable (see e.g. documents D22, page 347, column 1, second paragraph and page 348, column 1, "Box 1", D23, page 487, column 1, second paragraph).

18. Accordingly, in the board's view, the skilled person has all the necessary means at hand to assess whether or not a disorder falls within the ambit of the claims. Thus the board concludes that the subject-matter of claims 1, 3, 12, 14, and 16 and, hence, the main request as a whole meets the requirements of Article 84 EPC.

19. In view of the conclusion reached by the board in point 18 above, the arguments of appellant I (see section IX above) with regard to Article 84 EPC did not need to be considered.

Introduction to the invention

20. The present invention concerns diagnostic or therapeutic uses of protein kinase N beta (PKNbeta) and of agents directed against it. Active PI3-kinase increases the gene expression of PKNbeta (see example 12) which means that PKNbeta is a downstream target of the PI3-kinase/Phosphatase and tensin homolog (PTEN) signalling pathway (see paragraph [0029] of the patent).

21. The PI3-kinase/PTEN pathway plays a decisive role in regulating *inter alia* cell survival, growth, differentiation and motility in multi-cellular organisms (see e.g. document D17, page M22, column 1, third to fifth paragraph, figure 1, page M32, column 1, first paragraph). Constitutive activation of this pathway is *inter alia* associated with uncontrolled cell growth, i.e. a characteristic often found in cancer diseases (see e.g. document D23, abstract).

22. The PI3-kinase is an enzyme that is activated by extracellular stimuli, for example, platelet-derived growth factor (PDGF) in a receptor-mediated process which in response phosphorylates phosphatidylinositol (PI), a lipid present in cell membranes (see e.g. patent, paragraph [0087], document D15, Figure 10, and document D23, page 487, column 1, second paragraph to page 488, column 1, first paragraph). PTEN is the natural antagonist of PI3-kinase, which de-phosphorylates PI, *i.e.* the substrate of PI3-kinase, thereby terminating the PI3-kinase-mediated cellular functions.

Novelty (Article 54 EPC)

23. Objections under lack of novelty were raised by appellant II only with regard to claims 1 and 2 of auxiliary request 5 as maintained by the opposition division. These two claims have been deleted from the present main request which makes the objections moot.

24. Thus, the main request meets the requirements of Article 54 EPC.

Sufficiency of disclosure (Article 83 EPC)

25. Appellant II submitted as an issue of inventive step that the subject-matter of claims 1, 3, 11 to 16 and 20 did not solve the technical problem across the whole ambit of the claims. However, these claims are directed to the use of PKNbeta in either therapeutic or diagnostic applications, i.e. the technical effect of PKNbeta is expressed in the claims. In these circumstances it is the established case law of the boards of appeal that the issue of whether an effect is achieved over the whole ambit of the claims is to be assessed in the context of sufficiency of disclosure (see CLBA, section II.C.6.2, sixth paragraph). Since sufficiency of disclosure was a ground of opposition in the present case (see section II above), the board decided to deal with this issue under Article 83 EPC.

26. It is also established case law of the boards of appeal for a medical use claim to fulfill the requirements of Article 83 EPC, unless this is already known to the skilled person at the priority date, that the patent has to disclose the suitability of the product to be manufactured for the claimed therapeutic application. A

claimed therapeutic application may be proven by any kind of evidence as long as it reflects the therapeutic effect on which the therapeutic application relies (see CLBA, section II.C.6.2).

27. The board considers that by analogy thereto the same requirements of Article 83 EPC apply for diagnostic use claims.

28. The therapeutic application according to claims 11, 13 and 15 is "treatment and/or prevention of metastatic cancers". Hence, the therapeutic effect to be achieved by the use of agents directed against PKNbeta can be seen as the reduction or prevention of cancer in its metastatic stage. The question to be assessed is thus whether or not the evidence disclosed in the patent establishes this effect.

28.1 The patent discloses in examples 3 to 8 that antisense or siRNA molecules which either specifically reduce the gene expression of PKNbeta or interfere with the translation of mRNA into the corresponding protein sequence also prevent the spreading of prostate and HeLa tumour cells (see Figures 5 and 6). It was uncontested by appellant II, that spreading is a characteristic of metastatic cancers. Furthermore, Figure 1 of the patent discloses that PKNbeta is a down-stream member of the PI3-kinase pathway, in particular its mTOR-branch which is involved in tumour metastasis (see also paragraph [0087]).

28.2 Appellant II submitted as a first line of argument that the data disclosed in the patent did not demonstrate the suitability of inhibitors of PKNbeta in the therapy of metastatic cancers in general since the effect was shown in two metastatic cell lines only. In a second

line of argument the appellant submitted that these data showed that the inhibitors were effective, when PKNbeta was over-expressed. However, evidence that all metastatic cancers over-expressed PKNbeta was not derivable from the patent or the cited prior art documents. On the contrary, document D1 disclosed that solely three out of eight tumour cell lines exhibited an over-expression of PKNbeta's gene (see Figure 3).

28.3 The board is not convinced by these arguments. As regards the first line of argument, the patent discloses in examples 7 and 12 that the gene of PKNbeta is over-expressed in two metastatic cells lines. Thus, based on the evidence disclosed in the patent - and in the absence of evidence to the contrary - the board has no reason to doubt that the gene of PKNbeta is also over-expressed in other metastatic cancers. As regards the second line of argument, the board notes that document D1 discloses expression studies of the PKNbeta gene in eight cancer cell lines (see page 811, column 2, first paragraph, Figure 3) without however explicitly disclosing that these cell lines are metastatic. Since cancer cells are not necessarily all metastatic, this being a characteristic of a late tumour stage after the cells have accumulated numerous mutations and chromosomal deletions (see e.g. document D3, page 602, column 2, point 3.41 and Figure 3.79), it is not derivable from the disclosure of document D1 that the eight cell lines disclosed in Figure 3 are actually metastatic. Thus, the reported non-over-expression of PKNbeta in five of the eight tumour cell lines in Figure 3 of document D1 does not challenge the generic concept that PKNbeta is over-expressed in metastatic cancer cells.

29. Accordingly, in view of the experimental data disclosed in the patent, the board is satisfied that the suitability of inhibitors of PKNbeta in the therapy of metastatic cancers is demonstrated.

30. The diagnostic applications according to claims 1, 3, 12, 14 and 16 are "metastatic cancer and any pathological conditions involving the PI 3-kinase pathway" or "metastatic cancers" in claim 20. Hence, the effect to be achieved by the use of the compounds referred to in these claims is the detection of either metastatic cancers or of diseases involving the PI3-kinase pathway. The question to be assessed with regard to sufficiency of disclosure is thus whether or not the evidence reported in the patent establishes this effect.

30.1 The patent discloses in examples 7 and 12 that cancer cell lines with an activated PI3-kinase also over-express PKNbeta, which implies that PKNbeta is a downstream member of the PI3-kinase pathway. Moreover, the patent discloses that it was common general knowledge at its priority date that PI3-kinase is involved in tumour metastasis or in diseases involving the PI3-kinase pathway (see paragraphs [0035], [0036], [0038]). This is also supported by the disclosure of documents D17, D18 and D23 (see documents D17, page M26, column 2, point 3.5 to page M28, column 1, last paragraph, page M32, column 1, first paragraph; D18, page 85, Figure 1; D23, abstract).

30.2 Appellant II's arguments with regard to insufficiency of disclosure in relation to the diagnostic applications referred to in claims 1, 3, 12, 14, 16 and 20 were the same as those submitted in relation to the therapeutic applications (see point 28.2 above).

30.3 The board, for the reasons set out in point 28.3 above, is not convinced by these arguments of appellant II. Accordingly, the board is satisfied that the information disclosed in the patent demonstrates the suitability of the compounds referred to in claims 1, 3, 12, 14, 16 and 20 in the diagnosis of the disorders cited.

31. In a further line of argument relating to insufficiency of disclosure, appellant II submitted that the subject-matter of claims 1 and 3 relied on the use of labelled PKNbeta in competition assays, which were, however, not disclosed in the patent. Therefore, the skilled person would not have considered them as a means in the claimed diagnostic applications. Assuming that the skilled person would have taken them into consideration, the subject-matter of claims 1 and 3 could not be carried out across the whole ambit of the claims because their subject-matter was not limited to competition assays based on labelled PKNbeta.

32. The board is not convinced by this argument either. As regards the first part of it, it is established case law that common general knowledge may be used by the skilled person to supplement the information contained in the patent (see CLBA, II.C.3, third paragraph). Competition assays with labelled agents are routine in the diagnostic field, which was not contested by appellant II. Accordingly, the skilled person would have immediately contemplated these measures in carrying out the claimed invention. Furthermore, as regards the second part of the argument, since there is one way enabling the skilled person in relying on his common general knowledge to perform the claimed invention - and in the absence of evidence to the

contrary - the board reaches the conclusion that the invention can be considered as being performable in the whole range claimed (see CLBA, II.C.4.2 and 4.4).

33. Thus, the board concludes on the basis of the evidence on file that the main request meets the requirements of Article 83 EPC.

Inventive step (Article 56 EPC)

Closest prior art

34. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal normally apply the "problem and solution" approach. It requires as a first step the identification of the closest prior art. This is generally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most technical features in common, *i.e.* requiring a minimum of modifications (see CLBA, I.D.3.1).

35. The appellants considered either of documents D1 or D2 to represent the closest prior art.

36. Document D1 discloses that the gene encoding PKNbeta is over-expressed in three out of eight tumour cell lines tested, i.e. chronic myelogenous leukemia K-562, colorectal adenocarcinoma SW480 and HeLa cells, while its expression in normal human adult tissue is not elevated (see abstract and page 811, column 1, last paragraph and figure 3). The gene expression data suggest that PKNbeta may play a particular role in these immortalised cell lines (see page 811, column 2,

first paragraph). The document also discloses the use of polyclonal anti-PKNbeta antibodies in cellular localisation studies (see page 811, column 2, second paragraph) and that PKNbeta binds to RhoA under *in vitro* conditions (see page 811, column 1 first paragraph). However, document D1 is silent about therapeutic or diagnostic applications of PKNbeta, or about its involvement in tumour metastasis. Furthermore, the document does not disclose PI3-kinase, its signalling pathway or diseases associated therewith.

37. Document D2 discloses the isolation of 123 different protein kinases including PKNbeta (SEQ ID NOs: 133 and 134) which may be associated with 12 different diseases, *inter alia* cancer (see page 62, line 21 to page 63, line 25). Although document D2 reveals methods for detecting the gene expression of the kinases in samples for diagnostic purposes, guidance is not provided as to which of the kinases represents a suitable diagnostic marker in the specific diseases cited. Therefore document D2 discloses no link between PKNbeta and its use in the diagnosis of any of the cited diseases, in particular cancer. In the board's view, the skilled person in these circumstances would need to conduct research to establish such a link. Furthermore, the document remains silent with regard to metastatic cancer, PI3-kinase or diseases involving its pathway. Therefore, the board concludes that document D2 discloses no diagnostic application for PKNbeta, let alone a therapeutic one and does not qualify as closest prior art in line with the criteria set out in point 34 above.

38. Document D1, although not disclosing an explicit therapeutic or diagnostic application for PKNbeta,

reports that its gene is over-expressed in certain cancer cell lines when compared to normal, i.e. non-cancerous, human cells. This in the board's view, implies to the skilled person that PKNbeta is of potential diagnostic or therapeutic use in cancer, i.e. a purpose similar to that underlying the claimed invention.

39. Thus, the board concludes that document D1 represents the closest prior art.

Technical problem and solution

40. Claims 1, 3, 11 to 16 and 20 differ from the closest prior art either in their diagnostic or therapeutic applications thus providing specific diagnostic and therapeutic applications for PKNbeta.

41. Accordingly, the technical problem to be solved is formulated as the provision of further diagnostic and therapeutic applications for PKNbeta.

42. The board is satisfied that the solution provided by the subject-matter of claims 1, 3, 11 to 16 and 20 solves this technical problem.

Obviousness

43. It remains to be assessed whether or not the skilled person, starting from the over-expression of PKNbeta in certain cancer cell lines as disclosed in document D1 and faced with the technical problem defined above, would, either in view of this document alone or in combination with another teaching in the prior art, arrive in an obvious manner at the use of PKNbeta for the claimed diagnostic or therapeutic applications.

44. Document D1 suggests that over-expressed PKNbeta may play a role in particular immortalised cell lines, i.e. chronic myelogenous leukemia K-562, colorectal adenocarcinoma SW480 and HeLa cells (see page 811, column 2, first paragraph, Figure 3), without, however, specifying this role. Thus, for the reasons set out above (see point 28.3) the skilled person would not derive pointers from PKNbeta's gene expression in certain cancer cells as disclosed in document D1 that it is possibly involved in metastatic cancers too.

45. As regards PKNbeta's possible involvement in PI3-kinase-associated disorders, document D1 discloses that PKNbeta binds to RhoA under *in vitro* conditions and speculates that it may "*participate in the Rho-signaling pathway*" (see page 811, column 1, first paragraph). The skilled person furthermore knowing that RhoA is part of the PI3-kinase signalling pathway (see document D15, Figure 10), may therefore derive from the disclosure in document D1 that PKNbeta is likewise a part of this signalling pathway. However, document D1 is silent on the biological effects mediated by PKNbeta's binding to RhoA. The same applies to PI3-kinase and potential influences of this kinase on the observed binding between PKNbeta and RhoA, not to mention PI3-kinase's effects on PKNbeta's gene expression. Furthermore, the skilled person cannot predict - from the disclosed mere binding of PKNbeta to RhoA in document D1 - the kind of biological effects resulting therefrom. Thus, document D1 does not provide pointers that PKNbeta is a potential therapeutic target or a diagnostic marker for disorders associated with the PI3-kinase pathway either.

46. Accordingly, the board concludes that the subject-matter of claims 1, 3, 11 to 16 and 20 is not obvious in the light of the teaching of document D1 alone.

47. Appellant II submitted that the teaching in document D1 when combined with that of document D15 provided pointers that PKNbeta by its binding to RhoA was linked to the PI3-kinase pathway and involved in cell migration, i.e. a characteristic of cancer metastasis.

48. Document D15 discloses that the growth factor PDGF as an extracellular stimulus (see point 22 above) activates the PI3-kinase signalling pathway. PI3-kinase mediates by its regulatory and enzymatic subunits the inactivation of RhoA, causing a decreased amount of cellular stress fibres and focal adhesions, thereby promoting cellular migration, i.e. a property central *inter alia* in cancer metastasis (see Figure 10 on page 259, page 260, column 2, third paragraph). It further discloses that active RhoA inhibits cell migration (see page 249, column 2, second paragraph to page 250, column 1, first paragraph). Therefore, document D15 suggests that a PI3-kinase signalling pathway-mediated inactivation of RhoA contributes to metastatic spread of tumour cells by promoting cell migration, while active RhoA prevents metastasis by inhibiting cell migration. The document, however, is silent about PKNbeta and its potential involvement in cell migration. Moreover, such an involvement cannot be derived from the disclosed mere binding of PKNbeta to RhoA in document D1 either, since the skilled person cannot derive predictions about biological effects resulting therefrom. Thus, the combined teaching of documents D1 and D15 does not provide a pointer either to the skilled person that PKNbeta is potentially

involved in cancer metastasis and appellant II's argument does therefore not convince the board.

49. Accordingly, the board concludes that the subject-matter of independent claims 1, 3, 11 to 16 and 20 cannot be considered obvious in the light of the teaching of document D1 alone or in combination with that of document D15. The same applies to the subject-matter of claims 2, 4 to 10 and 17 to 19 all being dependent on the aforementioned claims.

50. Consequently, the main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the following claims and a description to be adapted thereto:

   Claims 1 to 20 filed as main request during the oral proceedings of 20 October 2016.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated