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**Datasheet for the decision
of 16 May 2007**

Case Number: T 0435/06 - 3.3.04

Application Number: 94922622.9

Publication Number: 0728143

IPC: C07K 5/00

Language of the proceedings: EN

Title of invention:
Oncoprotein protein kinase

Patentee:
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

Opponent:
CELLTECH R & D LIMITED

Headword:
Oncoprotein kinase/THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

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

Keyword:
"Main request: novelty (no)"
"Auxiliary request 1: added subject-matter (yes)"
"Auxiliary request 2: added subject-matter (no); broadening of
the scope of protection (no); novelty (yes)"
"Remittal (yes)"

Decisions cited:
-

Catchword:
-



Case Number: T 0435/06 - 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 16 May 2007

Appellant:
(Patent Proprietor) THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 9 January 2006
concerning maintenance of the European Patent
No. 0728143 in amended form.

Composition of the Board:

Chair: U. Kinkeldey
Members: R. Gramaglia
G. Weiss

Summary of Facts and Submissions

I. European Patent No. 0 728143 based on application No. 94 922 622.9 (published as WO 95/03324) filed on 18 July 1994 and claiming priority from US 94533 of 19 July 1993 and US 220602 of 25 March 1994 was granted on the basis of 36 claims, of which claims 35 and 36 read as follows:

"35. An isolated c-Jun N-terminal kinase (JNK) polypeptide **characterized by:**

(a) having a molecular weight of 55 kD as determined by reducing SDS-PAGE;

(b) having a serine and threonine kinase activity; and

(c) phosphorylating the c-Jun N-terminal activation domain;

wherein said polypeptide is not an ERK polypeptide."

"36. An isolated polynucleotide sequence encoding the polypeptide of claim 35".

II. Notice of opposition was filed by the opponent requesting the revocation of the European patent on the grounds of lack of novelty, lack of inventive step and insufficiency of disclosure (Article 100(a) and (b) EPC). The opposition was only against claims 35 and 36.

III. The opposition division maintained the patent on the basis of the claims of the auxiliary request then on file, no longer comprising the contested claims 35 and

36. The decision under appeal only dealt with the novelty issue.
- IV. The appellant (patentee) filed an appeal against the decision of the opposition division. The grounds of appeal filed with letter dated 19 May 2006 included a main request and auxiliary requests I to V.
- V. While claims 1 to 34 and 36 of the first and second auxiliary requests were the same as the corresponding granted claims, claim 35 of these requests differed from granted claim 35 (main request) in that further feature (d) had been added thereto, namely "(d) binding to c-Jun with specificity" (first auxiliary request) or "(d) binding to c-Jun GST fusion protein with specificity" (second auxiliary request), respectively.
- VI. The following documents are cited in the present decision:
- D1 Kyriakis J.M. et al., Journal of Biological Chemistry, Vol. 265, pages 17355-17363 (1990);
- D2 Pulverer B.J. et al., Nature, Vol. 353, pages 670-674 (1991);
- D5 Alvarez E. et al., Journal of Biological Chemistry, Vol. 266, pages 15277-15285 (1991);
- D6 Northwood I.C. et al., Journal of Biological Chemistry, Vol. 266, pages 15266-15276 (1991);
- D7 Chou S. et al., Molecular Biology of the Cell, Vol. 3, pages 1117-1130 (1992);

- D8 Minden A. et al., *Molecular and Cellular Biology*, Vol. 14, pages 6683-6688 (1994);
- D9 Hibi M. et al., *Genes & Development*, Vol. 7. pages 2135-2146 (1993);
- D10 Declaration by Dr Michael Karin dated 22 September 2005;
- D11 Declaration by Dr Roger J. Davis dated 21 September 2005;
- D12 Declaration by Dr Melanie H. Cobb dated 18 May 2006.

VII. The appellant's arguments in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarized as follows:

Main request

- The purification schemes described in document D1 would not lead to the isolation of pp54 MAP-2 kinase essentially free of other contaminant polypeptides since according to document D1 the pp54 MAP-2 kinase polypeptide was "the dominant component in the final isolate" and its specific activity was too low compared to the general specific activity ($> 1.0 \mu\text{mol}/\text{min}/\text{mg}$) of protein kinases purified to homogeneity.
- Since document D1 disclosed a plurality of purification methods, the cross-reference from

document D2 to document D1 could not be viewed as leading to a direct and unambiguous disclosure of the JNK2 protein of claim 35.

- The two kinases (pp54 MAP-2 and JNK2) could not be one and the same because the pp54 MAP-2 kinase of document D1 was capable of phosphorylating MAP-2 in the presence of polylysine, whereas the MAP-2 phosphorylation by JNK2 of claim 35 was not.

- The scientific data in documents D1/D2 were shown to be wrong by later documents D5 to D8, casting doubts that all the kinase proteins described in documents D1/D2 might have been contaminated with some undefined c-Jun N-terminal kinase activity.

Auxiliary request I

Article 123(2) EPC

- Feature (d) of claim 35 of this request had a basis on page 38, lines 18-20 of the published WO application.

Auxiliary request II

Article 123(2) EPC

- Feature (d) of claim 35 of this request had a basis on page 42, lines 9-17 of the published WO application.

Novelty

- Feature (d) of claim 35 of this request was not disclosed in the prior art.

VIII. The respondent's arguments during oral proceedings, insofar as they are relevant to the present decision, may be summarized as follows:

Main request

Novelty

- Documents D1 and D2 could be read together to assess the novelty of claim 35, since document D2 contained an explicit cross reference to document D1 and disclosed further characteristics of the protein isolated according to document D1.
- The pp54 MAP-2 kinase polypeptide described in documents D1/D2 exhibited all the features of the polypeptide of claim 35.

Auxiliary request I

Article 123(2) EPC

- The newly introduced feature (d) "binding to c-Jun with specificity" was not unambiguously derivable from the application as filed.

IX. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) or, alternatively, on the basis of one of the set of claims according to the auxiliary requests I to IV, filed with letter dated 19 May 2006.

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

Main request

Novelty

1. In simple words, claim 35 of this request requires that the claimed polypeptide (termed "JNK2") be isolated and should exhibit features (a), (b) and (c), wherein said polypeptide should not be an ERK polypeptide (see paragraph I supra).
2. As regards the feature "isolated", paragraph [0046] of the patent in suit defines such term as "essentially free of other polypeptides or other contaminants". The board observes that the "pp54 MAP-2 kinase" polypeptide disclosed in document D1 has undergone a "purification to near homogeneity" (see page 17355, r-h column, last paragraph). Moreover, the Table on page 17357 of this document shows a 10,011-fold purification for pp54 MAP-2 kinase and the SDS-PAGE of [γ -³²P]-labelled autophosphorylated pp54 MAP-2 kinase shows a single silver-stained band (see Fig. 2). Therefore, the terms "isolated" (claim 35) and "highly purified" (document D1) are *prima facie* synonymous.
3. Relying on declarations D10 (see section 7), D11 (see section 9) and D12 (see section 13), the appellant maintains that the purification schemes described in document D1 would not lead to the isolation of pp54 MAP-2 kinase essentially free of other contaminant polypeptides, as required by the wording of claim 35.

4. Emphasis is placed by the appellant on the sentence on page 17357, l-h column, last paragraph of document D1, according to which the 54 kDa polypeptide was "the dominant component in the final isolate". However, this passage has to be balanced with the expression "the highly purified kinase" in the same paragraph and with the sentence "the cycloheximide-stimulated MAP-2 kinase [i.e., the pp54 MAP-2 kinase] consists of a single 54-kDa polypeptide active as a monomer" (see page 17357, sentence bridging the l-h and r-h columns). It should also be noted that the 54 kDa polypeptide was the only species to exhibit ³²P incorporation upon incubation with [γ -³²P]ATP/Mg⁺⁺ (page 17357, l-h column, last paragraph), a sign that the enzyme was not significantly contaminated with exogenous substrates (see document D5, page 15278, bottom of r-h column).

5. It is also argued by the appellant that the specific activity of the pp54 MAP kinase polypeptide described in document D1 of 0.02 μ mol/min/mg (obtained by multiplying "21,724" (Table I) by "1 pmol/min = 1 U" (see page 17356, r-h column, lines 1-2; wherein 1 pmol = 10⁻¹² mol)) is too low, compared to the general specific activity (> 1.0 μ mol/min/mg) of protein kinases purified to homogeneity. However, there is no evidence before the board that the value ">1.0 μ mol/min/mg" referred to by the appellant has been measured using the same substrate used for pp54 MAP-2 (see page 17356, l-h column, under "MAP-2 Kinase Assays"), under conditions ensuring the "same phosphorylating activity" (see page 17358, r-h column, last full paragraph). No meaningful comparison can indeed be made if these conditions are not fulfilled. Nor is it possible to derive any data about the specific activity of the

- claimed JNK2 polypeptide from the patent in suit, of which paragraph [120] merely states that it binds c-Jun less efficiently than does the 46 kD protein (suggesting a lower specific activity). In any case, a feature defining the specific activity to be exhibited by the claimed JNK2 polypeptide is not present in claim 35.
6. In summary, the pp54 MAP-2 kinase described in document D1 satisfies the first requirement of claim 35 of this request that the claimed polypeptide should be "isolated".
 7. As for feature (a) in claim 35 ("molecular weight of 55 kD as determined by reducing SDS-PAGE"), the "pp54 MAP kinase" polypeptide described in document D1 is a "54-kDa polypeptide" (see page 17359, r-h column, third line under "Discussion" and the SDS-PAGE of Fig. 2). Therefore, the pp54 MAP kinase of documents D1/D2 and the polypeptide of claim 35 have the same molecular weight within the usual margin of error of $\pm 5\%$ for the molecular weight determination by SDS-PAGE. This has not been disputed by the appellant.
 8. As for feature (b) in claim 35 ("serine and threonine kinase activity"), it is stated in document D1 (see page 17359, r-h column, first line under "Discussion") that the "pp54 MAP kinase" polypeptide is a "Ser/Thr-specific protein kinase".
 9. Further, claim 35 requires that the claimed polypeptide is not an ERK polypeptide. The pp54 MAP kinase of document D1 is clearly distinct from pp42 and pp44, (renamed as ERK-2 and ERK-1, respectively) known from

the prior art (see e.g., document D1, page 17355, r-h column, line 10 and document D2, page 671, r-h column, lines 10-13).

10. In view of the above, the pp54 MAP kinase polypeptide described in document D1 exhibits all the features of the polypeptide of claim 35, exception made for feature (c), according to which the polypeptide should be "capable of phosphorylating the c-Jun N-terminal activation domain".

11. That the pp54 MAP kinase described in document D1 is also capable of phosphorylating the c-Jun N-terminal activation domain is shown in document D2, relating to further investigations on the "pp54 MAP kinase". It is indeed stated in document D2 (see page 670, abstract, lines 8-12) that their authors present "evidence that mitogen-activated protein-serine (MAP) kinases (pp54 and pp42/44) specifically phosphorylate these sites and that their phosphorylation positively regulates the transacting activity of c-Jun". Moreover, the Legend to Fig. 3 on page 672, l-h column of document D2 states that "MAP kinases specifically phosphorylate the two sites in the trans-activation domain of c-Jun".

12. The question arises whether documents D1 and D2 can be combined for assessing the novelty. In the legend to Fig. 3 on page 672, r-h column, line 14 from the bottom of document D2, it is stated that "pp54 MAP kinase was purified from rat liver as described⁷". On page 671, r-h column, lines 12-13 of document D2, reference is made again to "the recently identified pp54 MAP kinase⁷". Reference "⁷" of both passages is document D1. In the present case, the board considers that documents D1 and

D2 can legitimately be read together because document D2 contains an explicit cross-reference ("7") to document D1 when referring to the preparation method and the biological/chemical properties of the "pp54 MAP kinase".

13. The appellant maintains that since document D1 discloses a plurality of purification methods, the cross-reference from document D2 to document D1 cannot be viewed as leading to a direct and unambiguous disclosure of the JNK2 protein of claim 35.
14. The various purification methods in the appellant's view are a first purification scheme for the pp54 MAP kinase, as described on page 17356, l-h column, first and second paragraphs and a second purification scheme, as described on the same page, r-h column, second full paragraph entitled "Renaturation of MAP-2 Kinase Activity from SDS-Polyacrylamide Gels".
15. The board agrees that document D1 describes a first purification scheme summarised in Table I on page 17357, yielding the "highly purified" pp54 MAP kinase (see point 6 supra).

As regards the second purification scheme argued by the appellant, the paragraph headed "Renaturation of MAP-2 Kinase Activity from SDS-Polyacrylamide Gels" (see also the legend to Fig. 3) describes a process wherein 350 U of pp54 MAP kinase were denaturated with SDS and subjected to SDS-PAGE. The gels were sliced and a portion of each slice were subjected to extraction and renaturation, followed by an assay for MAP-2 kinase activity. The second full paragraph of the r-h column

on page 17356 concludes: "Routinely, 1-4% of the applied activity was recovered". Otherwise stated, the result of the second purification scheme pointed out by the appellant is 96-99% denaturated (i.e. devoid of biological activity) MAP-2 kinase.

16. To the mind of a skilled person willing to understand, not desirous of misunderstanding (see Case Law of the Boards of Appeal of the European Patent Office, 5th edition, 2006, page 205), the cross-reference from document D2 to document D1 ("pp54 MAP kinase was purified from rat liver as described⁷") can **only** mean that it is the 100% active fraction issued from the Mono-Q column (i.e., the first purification scheme summarised in Table I) which must be taken for further investigations on the enzymatic properties of pp54 MAP kinase, not the 96-99% denaturated protein from the SDS-polyacrylamide gel. Hence, this appellant's line of argument that documents D1 and D2 cannot be combined because document D1 discloses a plurality of purification methods, is not convincing.
17. In conclusion, since the pp54 MAP-2 kinase described in documents D1/D2 exhibits all the requirements/features set out in claim 35 of this request, the subject-matter of the claim lacks novelty and the main request is rejected.
18. The appellant argues that the pp54 MAP kinase preparation of document D1 is capable of phosphorylating MAP-2 in the presence of polylysine (see page 17359, r-h column, lines 12 to 44 and 52 to 54, according to which polylysine increased the activity of pp54 MAP-2 kinase 8-fold), whereas the MAP-

2 phosphorylation by JNK2 of claim 35 is not stimulated by polylysine (see document D9, page 2139, 1-h column, lines 7 to 11). Hence the appellant concludes that the two kinases cannot be one and the same.

But again, this feature is not relevant for distinguishing purposes since it is not in claim 35.

19. Finally the appellant points out that the scientific data in documents D1 and D2 were shown to be wrong by later documents D5 to D8. The appellant admits that this later discredit merely pertains to the ERK proteins (i.e., pp42/44 renamed ERK2 and ERK1, respectively), which turned out later on not to exhibit the capability announced in documents D1/D2 of phosphorylating the c-Jun N-terminal domain. Nevertheless it is the appellant's view that since the ERK proteins referred to in documents D1/D2 were possibly contaminated with a protein endowed with c-Jun-N-terminal-domain-phosphorylating activity, serious doubts arise about whether the above activity for the 54 kDa protein described in documents D1/D2 might likewise have included such contaminating activity.

However, in spite of the numerous documents cited by the appellant, there is no evidence before the board showing that the pp54 MAP kinase referred to in documents D1/D2 was devoid of c-Jun-N-terminal-domain-phosphorylating activity or that the preparations were contaminated with a protein endowed with this property.

First auxiliary request

Article 123(2) EPC

20. The claims of this request differ from those of the main request in that feature (d) "binding to c-Jun with specificity" has been added in claim 35 of the former request. The appellant maintains that this feature finds a basis on page 38, lines 18-20 of the WO application.

However, this passage merely relates to the specificity of the JNK protein kinase for at least one of the N-terminal sites of c-Jun, namely the capacity of phosphorylating at this site. But phosphorylation and binding are not necessarily linked together, as phosphorylation may also occur via a kinase cascade.

Article 54(2) EPC

21. Moreover, the newly introduced feature (d) "binding to c-Jun with specificity" is not a distinguishing feature since the pp54 MAP kinase described in documents D1/D2 also has this property (see document D2, page 673, 1-h column, line 2, referring to the "very high affinity of the kinase for this substrate").
22. In view of the non-compliance of claim 35 of this request with the requirements of Article 123(2) EPC and Article 54(2) EPC, this request must also be rejected.

Second auxiliary request

Article 123(2)(3) EPC

23. The claims of this request differ from those of the main request in that feature (d) "binding to c-Jun GST fusion protein with specificity" has been added in claim 35 of the former request. This feature has a basis on page 42, lines 10-17 of the WO application, describing an isolation method of the 55 kD kinase based on the specific binding to the c-Jun GST fusion protein and the successive elution of the kinase from the GSTcJun-agarose beads.

As for Article 123(3) EPC, no broadening of the scope of the granted claims occurs since claim 35 is now restricted to a protein additionally exhibiting feature (d) above.

Article 54(2) EPC

24. There is no evidence before the board that the "pp54 MAP kinase" dealt with in documents D1/D2 has the property of binding to the c-Jun GST fusion protein with specificity. Consequently the subject-matter of claims 35 and 36 satisfies the requirements of Article 54(2) EPC.

Remittal

25. The present patent was maintained on the basis of claims different from the claims presently on file (see paragraph III supra). For the purpose of the present decision the board has already examined the claims as to whether they fulfil the requirements of

Articles 123(2)(3) and 54(2) EPC (see points 23 and 24 supra), but, in order not to deprive the appellant of the possibility to have his invention examined by two instances, and in accordance with the established jurisprudence of the boards of appeal, the board uses its discretion under Article 111(1), second sentence, EPC, and remits the case to the first instance for further prosecution to consider the remaining issues.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance for further prosecution on the basis of claims 1 to 36 of the second auxiliary request filed with letter of 19 May 2006.

The Registrar:

The Chair:

P. Cremona

U. Kinkeldey