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Datasheet for the decision of 30 May 2007

Case Number: T 0757/06 - 3.3.08

Application Number: 95902574.3

Publication Number: 0730646

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Protein Tyrosine Kinases named Rse

Applicants
GENENTECH, INC., et al

Opponent:
-

Headword:
Rse kinases/GENENTECH

Relevant legal provisions:
EPC Art. 56, 123(2)

Keyword:
"Main request: lack of inventive step (yes)"
"Auxiliary request: added matter (yes)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0757/06 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 30 May 2007

Appellants: GENENTECH, INC.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 5 December 2005 refusing European application No. 95902574.3 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

I. The applicants (appellants) lodged an appeal against the decision of the examining division of 5 December 2005 refusing the European patent application No. 95 902 574.3 with publication number 0 730 646. The application entitled "Protein Tyrosine Kinases Named Rse" originated from an international patent application published as WO 95/14776 (referred to in the present decision as the "application").

II. In a decision dated 1 April 2004, the examining division refused the application. The appellants lodged an appeal against that decision. The examining division rectified its decision under Article 109(1) EPC and continued the proceedings. On 5 December 2005, the examining division again refused the application.

III. The later decision was based on the main request filed with the letter of 15 April 2003 (claims 1 to 19) and the auxiliary request as referred to in the letter of 16 January 2004 (claims 1 to 18 of the main request). Reasons for the refusal were lack of inventive step for both requests and lack of disclosure as regards the invention according to claim 19 of the main request.

IV. On 12 April 2006, the appellants filed a statement setting out the grounds of appeal which was accompanied by a main and an auxiliary request which exactly corresponded to the requests on which the decision under appeal was based. A refund of the appeal fee was requested on the ground that a substantial procedural violation had been committed.

V. The examining division did not rectify its decision and referred the appeal to the Board of Appeal (Article 109 EPC).

VI. A communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal presenting some preliminary and non-binding views of the Board was sent to the appellants.

VII. In reply thereto, the appellants filed on 30 April 2007 a new main request and a new auxiliary request to replace the requests on file. The main request (claims 1 to 18) corresponded exactly to the first auxiliary request as refused by the examining division.

VIII. At the oral proceedings which were held on 30 May 2007, the appellants filed a new first auxiliary request (claims 1 and 2) designated as the "second replacement auxiliary claim request 1" to replace the auxiliary request on file.

IX. Claim 1 of the respective requests at issue reads as follows:

(a) Main request

"1. An isolated polypeptide comprising a Rse receptor protein tyrosine kinase (rPTK) possessing a biological property of rPTK and having the amino acid sequence set out in Figure 1A or Figure 1B."

(b) First auxiliary request

"1. An isolated ligand capable of binding the extracellular domain of Rse receptor protein tyrosine kinase (rPTK) and of inducing receptor autophosphorylation wherein the ligand is an antibody or Rse rPTK binding fragment thereof, wherein the Rse rPTK comprises the amino acid sequence of residues 41 onwards in fig. 1A, and wherein the extracellular domain consists of residues 41 to 428."

X. The following documents are referred to in the present decision:

(D1) Melanie R. Markt et al., The Journal of Biological Chemistry, Vol. 269, No. 14, 8 April 1994, Pages 10720 to 10728

(D7) Steven K. Hanks et al., Science, Vol. 241, 1 July 1988, Pages 42 to 52

(D8) Cary Lai and Greg Lemke, Neuron, Vol. 6, May 1991, Pages 691 to 704

(D17) C. Lai and G. Lemke, Society for Neuroscience Abstracts, Molecular and Pharmacological Correlates of Development II, 25 October 1992, Page 238, Abstract No. 111.15

(D18) Leslie G. Biesecker et al., Proc. Natl. Acad. Sci. USA., Vol. 90, August 1993, Pages 7044 to 7048

(D22) EMBL-EBI sequence version archive with accession number X72886, issued on 1 September 1993

(D25) Andrew F. Wilks, Proc. Natl. Acad. Sci. USA., Vol. 86, March 1989, Pages 1603 to 1607

XI. The submissions made by the appellants, insofar as they are relevant to the present decision, may be summarised as follows:

Main request (inventive step)

The technical problem with which the skilled person was faced might be seen as the provision of new receptor-type tyrosine kinases.

Document D7 observed (see the concluding paragraph "Perspectives" on page 51) that confirming protein kinase activities for newly identified family members as well as elucidating their functional roles were difficult tasks.

There were two reasons why the skilled person aiming at identifying new receptor-type tyrosine kinases would not have started from the partial rat tyro-3 sequence referred to in document D8. Firstly, it would have been difficult to differentiate between homologous receptor tyrosine kinases. Secondly, the partial tyro-3 sequence (see Figure 2 of document D8, block VIII of amino acid residues) was not the best candidate among the other partial sequences disclosed in document D8. Indeed, in contrast to the other tyro sequences, it had a leucine (L) residue instead of a methionine or threonine (M/T) residue within the highly conserved PTK-specific motif (K/R)W(M/T)APES (as identified in the passage bridging pages 1605 and 1606 of document D25).

The skilled person would not have regarded it as relevant to combine the teaching of document D17, in which document D8 was referred to, with that of either document D18 in respect of the murine receptor or document D22 in respect of the human receptor. In fact, document D18 left open the question of whether any putative murine protein kinases incorporating the partial sequences referred to therein were in fact receptors (see the last sentence of the first full paragraph on page 7048). Document D22 disclosed only a 816 base-pair mARN sequence of a human tyro-3 tyrosine kinase but did not contain any information useful to identify it as a receptor.

In any case, document D17 was irrelevant in that the rat tyro-3 tyrosine kinase of document D8 was presented as only a **putative** receptor. Therefore, the skilled person would have simply discarded it.

Auxiliary request (added matter)

Support existed for the ligand of claim 1 in the experimental part of the description, in particular in Example J (see page 66) which illustrated the generation of one such ligand in the form of polyclonal antibodies prepared against a fusion protein consisting of the extracellular domain of the human Rse protein and an immunoglobulin and Example K (see also page 66) which showed that those polyclonal antibodies were capable of stimulating the autophosphorylation of the human Rse protein.

XII. The appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 18 of the main request filed on 30 April 2007 or claims 1 and 2 of the first auxiliary request filed during the oral proceedings. A refund of the appeal fee was no longer requested.

Reasons for the decision

Main request

1. Claim 1 is directed to an isolated polypeptide comprising a Rse receptor protein tyrosine kinase (rPTK) possessing a biological property of rPTK and having the amino acid sequence of the human Rse protein or the murine Rse protein as set out in Figures 1A and 1B, respectively.

2. As the expected endogenous ligands have not been identified in the application, the Rse protein either in its human or murine form of claim 1 is to be regarded as a **putative** receptor. This is in line with the admission made in this respect in the post-published document D1 (see in particular the abstract on page 10720), which is the scientific publication of the present application (expert opinion).

3. At the priority date much effort had been directed toward isolation and study of tyrosine kinases as illustrated by a number of publications in scientific journals some of which, including document D8, are referred to in the application (see pages 1 to 5).

4. In particular, document D8 describes a survey which led to the identification of 6 protein-tyrosine kinase genes (tyro-1 to -6) predominantly expressed by distinct sets of neural cells of the **rat**, tyro-3 showing **intense hybridization** to **brain** mRNA (see the first paragraph of the left-hand column of page 697). Amino acid sequences were deduced from the nucleotide sequences of the different PTK domain cDNAs encountered in the survey. They are represented in Figure 2 (see page 693). The suggestion is made that those genes are likely to encode cell surface **receptors** (see left-hand column on page 700).

5. The finding that **the tyro-3 protein** was a putative **receptor** tyrosine kinase was later confirmed by the same authors of document D8 in document D17.

6. Document D17, the content of which includes the teaching of document D8, to which explicit reference is made, is considered to represent the closest state of the art. The technical problem to be solved by the invention is regarded as being the provision of further **receptor**-type kinases, in particular tyro-3 homologues from **brain** tissue of other species.

7. The question to be answered is whether the skilled person would have found any incentive in the state of the art to look for human and murine homologues of the rat tyro-3 putative receptor tyrosine kinase.

8. A straightforward search in the literature (e.g. a bibliographic survey based on the terms "tyro-3" and "tyrosine kinase") would have directed the skilled person to document D22. This document is a file from

the EMBL-EBI sequence databank which discloses a 816 base-pair sequence which is presented as a human mRNA submitted by a search team including the authors of documents D8 et D17 coding for a human tyrosine kinase designated tyro-3. Furthermore, document D8 is referred to as a citation in document D22.

9. A further similar literature search would have drawn the skilled person's attention to document D18, which reports the identification of four murine cDNAs encoding putative protein kinases from primitive embryonic stem cells. Document D18 describes partial protein sequences and acknowledges that one of them, referred to as ETK-2, is identical to the **rat tyro-3** of document D8 which is citation 25 (see the note in the right-hand column of page 7048). It also states that the ETK-2 gene has a highly restricted expression pattern, being present in particular in the **brain**, an expression pattern which is regarded by the authors as consistent with that of a **receptor** (see the second full paragraph in the left-hand column of page 7048).

10. In the Board's judgment, starting from the partial tyro-3 nucleotide sequences of documents D22 and D18, by applying conventional techniques the skilled person would have been in a position to isolate complete cDNA clones and to deduce and express therefrom full length tyro-3 tyrosine kinases. Their putative receptor role, already envisageable on the basis of homology with the rat tyro-3 would have also been easily assessable based on the known ligand-mimicking technique with antibodies (see page 61, lines 19 to 26 in the application). Thus, the subject-matter of claim 1 would have been achieved

by the skilled person without the exercise of inventive skill.

11. The argument made by the appellants that the skilled person would not have considered the tyro-3 partial amino acid sequence of document D8 but rather another tyro sequence described therein is not tenable. It is true that the tyro-3 protein differs from previously described kinases in the highly conserved PTK-specific motif (K/R)W(M/T)APES, this is also the case for the deduced amino acid sequences tyro-1, tyro-2, tyro-4, tyro-5 and tyro-6, which each differs from that sequence at least in one position. There is however a positive statement in document D8 (see point 4 ***supra***) in favour of tyro-3 reporting that it has shown **intense hybridisation** to **brain** mRNA. This would certainly have drawn the skilled person's attention. Moreover, document D17 has confirmed that the rat tyro-3 tyrosine kinase was a putative receptor. Therefore, in the Board's view, the rat tyro-3 partial amino acid sequence would have been considered by the skilled person as the best candidate to start with.

First auxiliary request

12. Claim 1 is directed to an antibody or a fragment thereof capable of binding the extracellular domain of the human Rse receptor and of inducing autophosphorylation of that receptor, wherein the said protein comprises the amino acid sequence from 41 onwards shown in Figure 1A and the extracellular domain consists of residues 41 to 428.

13. The appellant has indicated that a support existed for the claimed subject-matter in the experimental part of the description in the application as filed, primarily in Examples J and K (see page 66 of the application).

14. In the experiment reported in Example K, 3T3.gD.R11 cells, i.e. cells capable of expressing two glycoforms of 120 kDa and 140 kDA, respectively, of the gD-Rse protein, or control NIH3T3 cells were exposed to preimmune serum or polyclonal antisera generated against the fusion protein Rse-IgG.

14.1 These polyclonal antisera have been generated as indicated in Example J (see page 66). gD-Rse is a protein consisting of the human Rse protein fused at its N-terminal portion with the first 53 aminoacid residues of the precursor of the herpes simplex virus Type I glycoprotein (gD) (see Example B on page 60). Rse-IgG is also a fusion protein. It consists of the extracellular domain of the human Rse protein fused at its N-terminal portion with the human IgG-γ1 heavy chain (see Example F on page 64).

14.2 In Example K, it is indicated that treatment of the 3T3.gD.R11 cells with anti-Rse ECD antisera, i.e. those antibodies contained in the polyclonal antisera generated against the ECD moiety of the Rse-IgG protein, stimulated the phosphorylation of the 140 kDa gD-Rse protein.

15. From the above analysis it results that Example K relates to antibodies as part of antisera generated against a particular fusion protein, namely Rse-IgG

which were shown to induce **phosphorylation** of the particular 140 kDa gD-Rse fusion protein.

16. The subject-matter of claim 1 is not limited to such particular arrangements as the antibody therein claimed is of a much broader outline not being limited to the particular fusion variants of the example.

17. As no other passage in the application as filed has been indicated by the appellants which could support such a generalisation, the Board concludes that the passages in the application as filed referred to by the appellants do not provide a support for the subject-matter of claim 1. Therefore, claim 1 contains subject-matter which extends beyond the content of the application as filed and does not comply with the requirements of Article 123(2) EPC. Thus, the first auxiliary request should also be refused.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani