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Datasheet for the decision of 6 December 2011

Case Number: T 1980/08 - 3.3.08

Application Number: 95926279.1

Publication Number: 0773997

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Htk Ligand

Patentee:
Genentech, Inc.

Opponent:
STRAWMAN LIMITED

Headword:
Transmembrane Htk ligand/GENENTECH

Relevant legal provisions:
EPC Art. 54(1)(3), 56, 83

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main and sole request - novelty, inventive step, sufficiency of disclosure (yes)"

Decisions cited:
-

Catchword:
-

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Case Number: T 1980/08 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 6 December 2011

Appellant: (Opponent)
STRAWMAN LIMITED
34 Lovedon Lane
Winchester
Hampshire SO23 7NU (GB)

Representative:
Mercer, Christopher Paul
Carpmaels & Ransford
One Southampton Row
London WC1B 5HA (GB)

Respondent: (Patent Proprietor)
Genentech, Inc.
460 Point San Bruno Boulevard
South San Francisco CA 94080 (US)

Representative:
Walton, Seán
Mewburn Ellis LLP
33 Gutter Lane
London EC2V 8AS (GB)

Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted on 18 August 2008 concerning maintenance of European patent No. 0773997 in amended form.

Composition of the Board:

Chairman: M. Wieser
Members: P. Julià
R. Moufang

Summary of Facts and Submissions

I. European patent no. 0 773 997 is based on European patent application no. 95 926 279.1, filed as International patent application and published as WO 96/02645 (hereinafter "*the application as filed*"). The patent was opposed on the grounds as set forth in Articles 100(a) and (b) EPC.

II. The opposition division considered a main request filed on 20 March 2008 not to fulfil the requirements of Article 54(3) EPC and an auxiliary request filed on 21 May 2008 to fulfil the requirements of the EPC. Accordingly, the patent was maintained on the basis of this auxiliary request (Article 101(3)(a) EPC).

III. The opponent (appellant) filed a notice of appeal and a statement setting out its grounds of appeal together with two new documents (D8 and D9). Oral proceedings were requested as a subsidiary measure.

IV. The patentee (respondent) replied to the appellant's grounds of appeal and requested that the appeal be dismissed and the patent be maintained on the basis of the auxiliary request allowed by the opposition division. If documents D8 and D9 were to be introduced into the appeal proceedings, a remittal of the case to the first instance was requested. Oral proceedings were also requested as a subsidiary measure.

V. On 31 May 2011, the parties were summoned to oral proceedings and, in a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached thereto, informed of the

board's preliminary, non-binding opinion on the substantive issues of the appeal.

VI. On 15 September 2011, the appellant withdrew its subsidiary request for oral proceedings and informed the board of its intention not to attend the upcoming oral proceedings. No substantive submissions were made in reply to the board's communication.

VII. On 18 October 2011, the respondent replied to the board's communication replacing its main request, which was made its first auxiliary request, by a replacement main request and pages 3, 20, 23 and 25 of the description adapted thereto. In the respondent's view, oral proceedings were not necessary but, in the event that the board had objections to its replacement main request, it intended to attend.

VIII. On 27 October 2011, the parties were informed that the oral proceedings appointed for 22 November 2011 were cancelled.

IX. The respondent's replacement main request consisted of 13 claims. Claims 1 and 12 read as follows:

"1. An isolated protein molecule which binds to the Htk receptor and which induces phosphorylation of the Htk receptor, the molecule comprising the amino acid sequence for mature murine Htk ligand of SEQ ID NO: 2."

"12. A monoclonal antibody which binds to an isolated protein molecule which binds to the Htk receptor and which induces phosphorylation of the Htk receptor, the amino acid sequence of the

protein molecule being the amino acid sequence for mature murine Htk ligand of SEQ ID NO: 2 or the amino acid sequence for mature human Htk ligand of SEQ ID NO: 4; or

an isolated soluble Htk ligand which binds to the Htk receptor, the amino acid sequence of the soluble Htk ligand being the amino acid sequence for mature soluble murine Htk ligand of amio acids 28-227 of SEQ ID No 2 or mature soluble human Htk ligand of amino acids 25-224 of SEQ ID No 4;

wherein the monoclonal antibody

is labelled, optionally with a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I, a fluorescent or chemiluminiscent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase;

is a humanized antibody;

is a human antibody;

is an antibody fusion with a heterologous protein;

is an antibody fragment which binds to the protein molecule which binds to the Htk receptor, e.g. Fab, $F(ab')_2$ or Fv;

is bispecific; or

is a heteroconjugate antibody."

Claims 2 and 3 were directed, respectively, to an isolated mature soluble murine Htk ligand of amino acids 28-227 of SEQ ID NO: 2 and to a composition comprising the proteins of claims 1 or 2 and a pharmaceutically acceptable carrier. Claims 4 to 7 were directed to isolated nucleic acid molecules encoding the proteins of claims 1 or 2. Claims 8 and 9 related, respectively, to a vector comprising the nucleic acid

molecule of any one of claims 4 to 7 and to a host cell comprising said vector. Claim 10 was directed to a method of preparing a protein which induced phosphorylation of the Htk receptor comprising culturing a host cell transfected to express the nucleic acid molecule of claim 9 and recovering said protein molecule from the host cell culture. Claim 11 was directed to a method for activating "*in vitro*" a tyrosine kinase domain of a hepatoma transmembrane kinase receptor (Htk receptor) comprising contacting an extracellular domain of Htk receptor with the Htk ligand of any one of claims 1 or 2. Claim 13 was directed to a method of producing a monoclonal antibody which bound to the isolated protein or the isolated soluble Htk ligand defined in claim 12.

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

D1: WO 96/01839 (publication date: 25 January 1996; priority date: 8 July 1994);

D2: WO 93/15201 (publication date: 5 August 1993);

D3: B.D. Bennett et al., J. Biol. Chem., Vol. 269, No. 19, 13 May 1994, pages 14211 to 14218;

D4: T.D. Bartley et al., Nature, Vol. 368, 7 April 1994, pages 558 to 560.

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

Admissibility of documents D8 and D9 into the appeal proceedings

(No submissions were made either to explain why these documents were introduced into the appeal proceedings and not at a much earlier stage in the opposition proceedings, or to support their relevance over other prior art on file).

Article 100(b) EPC/Article 83 EPC

Not even a single (classical or engineered) antibody which bound to a Htk ligand was exemplified in the patent-in-suit and there was no example of any of the types of monoclonal antibodies listed in claim 12. Whereas the production of monoclonal antibodies might have been routine, the production of the specific types of monoclonal antibodies cited in claim 12, such as human monoclonal antibodies, was not routine in 1994.

Article 100(a) EPC/Article 54(3) EPC

Document D1 disclosed monoclonal antibodies against human LERK-5 proteins (Htk ligand of the patent) using techniques known in the art. Hybrid antibodies were not limited to those whose variable and constant domains were from different species. Thus, document D1 disclosed (classical) hybrid monoclonal antibodies and claims 12 and 13 (directed to a method of producing the monoclonal antibodies of claim 12) were not therefore novel.

Article 100(a) EPC/Article 56 EPC

Both documents D2 and D3 related to the same technical field as the patent-in-suit (identification of Eph receptor kinase family members and their functional role) and thus, could represent the closest prior art document. Document D3 disclosed a new member of the Eph subfamily, namely the Htk receptor protein tyrosine kinase referred to in the patent-in-suit. The presence of tyrosine kinase activity and the induction of phosphorylation by interaction of Htk with an antibody (directed against its extracellular domain) suggested that the disclosed new member was a signal transducing molecule, a receptor for a ligand triggering kinase activation. Document D3 stated that no ligand had yet been identified for the members of the Eph receptor proteins and indicated that structural analysis of Htk and the identification of its ligand were required for defining its biological role. Document D2 also disclosed the Htk receptor protein tyrosine kinase of the patent-in-suit (named HpTK5) and stated that ligands of this receptors could be identified using standard laboratory techniques.

Starting from this prior art, the technical problem to be solved was the provision of a ligand for the Htk (HpTK5) receptor. The human Htk (HpTK5) ligand of the patent-in-suit solved this problem. However, this solution was obvious in the light of the common general knowledge or in combination with document D4.

Methods for identifying and cloning novel genes were known in the art (screening a cDNA/genomic library with a selected probe, PCR methodology, etc) and both

documents D2 and D3 provided sufficient information as to the location of the Htk (HpTK5) receptor to enable the skilled person to select a suitable DNA source (fetal brain tissue as cited in the patent) for carrying out said cloning. Following the teachings of documents D2 or D3, the skilled person had a motivation to identify the Htk (HpTK5) ligand and standard techniques were available to do so. No inventive skill was thus required to identify the Htk (HpTK5) ligand.

Document D4 disclosed the isolation of B61, a ligand for the Eck receptor protein tyrosine kinase (a member of the Eph/Eck family), using the extracellular domain of the receptor as an affinity agent. Although B61 had only 23.08% similarity to the Htk ligand of the patent, document D4 disclosed a method for identifying an Eph/Eck ligand to its cognate receptor. Thus, it would have been obvious for the skilled person to use this method with the Htk (HpTK5) receptor of documents D2 or D3 and identify thereby a cognate ligand having the structural and functional properties of the Htk ligand. Both B61 and the Htk ligand were membrane bound, the former via a glucosylphosphatidylinositol (GPI)-anchor and the latter via a transmembrane domain. There was no reason that the method of document D4 should not be appropriate for identifying the transmembrane Htk ligand. Although in the patent-in-suit the Htk ligand was isolated from cells rather than from a supernatant, proteases in the extracellular milieu were able to cleave membrane-bound proteins and release soluble parts thereof. In the preparation of cell culture supernatants, membrane-bound ligands could be cleaved by these proteases and soluble ligands released in the supernatant. Thus, extracellular parts of

membrane-bound ligands could be found in a cell culture supernatant, as shown in document D4 by the presence of the released part of the GPI-anchored B61 ligand in the cell culture supernatant.

Once a human ligand was isolated, the isolation of cognate ligands from other species (mouse) was obvious. Thus, on the basis of documents D2 or D3 in combination with the common general knowledge or with document D4, the isolation of the human and/or murine Htk (HpTK5) ligand was obvious and it was a matter of routine to raise classical monoclonal antibodies thereto using standard procedures.

XII. The submissions made by the respondent, insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of documents D8 and D9 into the appeal proceedings

No explanation had been provided to justify the introduction of these late-filed documents into the appeal proceedings. None of them changed the fact that the claimed subject-matter was novel, inventive and supported by the disclosure of the patent.

Article 100(b) EPC/Article 83 EPC

The objection of insufficiency of disclosure was based on the breadth and clarity of the claims. However, the appellant had not discharged its burden of proof on this ground and no objective reasons substantiated by verifiable facts had been put forward for doubting the

sufficiency of disclosure. There was prior art on file showing that techniques (hybridoma and non-hybridoma technology, such as phage display) were known in 1994 for making monoclonal antibodies and, in particular, human monoclonal antibodies.

Article 100(a) EPC/Article 54(3) EPC

Document D1 disclosed monoclonal antibodies produced by a method characterized only by immunising mice and generating hybridomas. Claims 12 and 13 contained features of the method of manufacture disclosed in the patent which were not present in document D1. An antibody comprising its natural pairing of chains and domains was not an hybrid antibody. Claim 13 required to produce the antibody by recombinant DNA methods, from a phage library or from a transgenic mouse capable upon immunization of producing human antibodies. None of these methods were disclosed in document D1.

Article 100(a) EPC/Article 56 EPC

Document D3 contained some functional analysis of the disclosed Htk receptor and a discussion of mimicking ligand action. There was no functional analysis of the HpTK5 receptor disclosed in document D2 which contained only a vague statement that ligands could be identified. Thus, document D3 represented the closest prior art document providing a preliminary characterization of a novel orphan receptor with no ligand identified. This document referred to the fact that no ligands had yet been identified for members of the EPH transmembrane protein family and it further described an experiment with a chimeric protein (using the Elk intracellular

portion and the extracellular domain of the EGF receptor) with an EGF-induced effect on cell growth. Significantly, EGF was a soluble ligand, illustrating what was also expected for the Htk ligand. Although document D3 acknowledged that the structural analysis of Htk and the identification of its ligands were required for defining its biological role, there was no indication about how this had to be done.

No evidence in the form of "encyclopaedias, textbooks, dictionaries and/or handbooks" (i.e. common general knowledge) was on file to be combined with document D3. Only speculations were made on what the skilled person would have done. For a realistic consideration, only the combination of documents D3 and D4 came into question. Document D4 identified the B61 protein as an ECK ligand (ECK being a member of the orphan EPH receptor protein tyrosine kinase family) and suggested the isolation of B61-related ligands for other members of this EPH family in the same way as disclosed in document D4. However, although (recombinant) B61 could be associated with the membrane via GPI (and thus could interact, as it indeed did, with other members of the EPH/ECK receptor family), B61 had no transmembrane region and had a low (23.08%) similarity to the Htk ligand disclosed in the patent-in-suit. However, it was, and had to be, identified in a different way than said Htk ligand. There was no prior art on file suggesting the Htk ligand to be a transmembrane protein. The combination of document D3 with prior art concerned with transmembrane (ligand) proteins required hindsight.

Document D3 reported that no ligands had been found for any member of the EPH/ECK receptor family and, by

reference to EGF experiments, expected a soluble ligand for the Htk receptor. Document D4 concerned a different molecule and there was evidence in the patent-in-suit to indicate that the skilled person, following the teachings of document D4 to look for the Htk ligand, would have failed. The identification of the Htk ligand was a rare success outnumbered by many more failures and, accordingly, required inventive skill.

XIII. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

XIV. The respondent (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the replacement main request and pages 3, 20, 23 and 25 of the description adapted thereto all filed on 18 October 2011 and pages 4, 5 and 21 as filed on 21 May 2008 and pages 2, 6 to 19, 22, 24 and 26 to 32 of the patent-in-suit.

Reasons for the Decision

Scope of the appeal proceedings

1. In the communication of the board pursuant to Article 15(1) RPBA (cf. Section V *supra*), the claims of the auxiliary request considered allowable by the opposition division which were contested by the appellant in the grounds of appeal were identified by the board as:

i) claims 3 and 5 for added subject-matter (Article 100(c) EPC/Article 123(2) EPC),

ii) claim 17 for insufficiency of disclosure (Article 100(b) EPC/ Article 83 EPC),

iii) claims 3 to 9, 13 to 15 and 17 to 18 for lack of novelty over document D1 (Article 100(a) EPC/Article 54(3) EPC), and

iv) claims 1 to 18 for lack of inventive step (Article 100(a) EPC/Article 56 EPC), when considering documents D3 or D2 as the closest prior art in combination with the common general knowledge or with documents D4 or D8.

The board concluded that the appellant contested the auxiliary request considered allowable by the opposition division in its entirety and on the basis of all grounds of opposition (Articles 100(a), (b) and (c) EPC).

2. In the respondent's replacement main request filed on 18 October 2011, claims 3 to 7 of the auxiliary request considered allowable by the opposition division were deleted and the contested embodiment of claim 17 of this auxiliary request (wherein the monoclonal antibody was defined as an "*hybrid antibody which has a variable domain spliced with a constant domain*") was deleted in the corresponding claim of the main request (claim 12).

3. In view of these amendments introduced into the respondent's replacement main request, the objections raised under Article 100(c) EPC (Article 123(2) EPC) no longer apply.

Admissibility of documents D8 and D9 into the appeal proceedings

4. According to Article 12(4) RPBA, it is within the power of the board to hold inadmissible facts, evidence or requests which could have been presented in the first instance proceedings. No explanation has been given by the appellant for introducing documents D8 and D9 at this stage of the proceedings and there is no apparent reason which could have prevented the appellant from introducing them at a much earlier stage in the opposition proceedings.

5. Document D8 is a scientific document published in December 1993 and thus, more than half a year earlier than the priority date of the patent-in-suit. In the appellant's grounds of appeal, document D8 is cited only in the context of Article 56 EPC and as a possible alternative to document D4 for a combination with the closest prior art documents D2 or D3.

6. Document D9 is a review article published in 2000 and thus, after the filing date of the patent-in-suit. In the appellant's ground of appeal, document D9 is cited only in the context of Article 83 EPC. In this context, reference is also made to other prior art documents on file. It is not evident that document D9 is more relevant than this prior art.

7. In view of the above considerations and in the absence of further submissions from the appellant, which was made aware of these deficiencies and questions in the board's communication pursuant to Article 15(1) RPBA (cf. Section V *supra*), documents D8 and D9 are not admitted into the appeal proceedings.

Article 100(b) EPC/Article 83 EPC

8. In the board's communication pursuant to Article 15(1) RPBA, it was noted that the appellant's objection under Article 100(b) EPC/Article 83 EPC is, in essence, directed to the broadness of present claim 12 and, more particularly, to the embodiment of a "*human monoclonal antibody*", allegedly due to the difficulties encountered in its production. This objection is different from that dealt with by the first instance for arriving at its decision on the issue of sufficiency of disclosure (cf. pages 8 and 9, point 17 in the decision under appeal). Neither the decision under appeal nor the minutes of the oral proceedings before the opposition proceedings contain any comments regarding the difficulties encountered in the production of human mAb now alleged by the appellant.

9. Indeed, this objection was not raised in the notice of opposition but only, in a very general manner, in a letter dated 20 March 2008 filed by the opponent/appellant in reply to the summons to oral proceedings issued by the opposition division (cf. page 3, third paragraph from the bottom). However, in this letter it was also stated, when arguing against inventive step, that it was standard practice to produce the specific types of monoclonal antibodies

referred to in the claims (cf. page 5, last two paragraphs and page 7, second to fourth paragraphs in opponent/appellant's letter of 20 March 2008). No comments were made to the now alleged technical difficulties in the production of human mAbs.

10. In the light of the evidence on file, the board considers that appellant's objection does not meet the criteria established by the case law for it being successful, namely the presence of serious doubts substantiated by verifiable facts (cf. "Case Law of the Boards of Appeal of the EPO", 6th edition 2010, II.A.7, page 250). The requirements of Article 83 EPC are considered thus to be fulfilled.

Article 100(a) EPC/Article 54(3) EPC

11. It is not contested that SEQ ID NO: 4 of the patent-in-suit (human Htk ligand) and SEQ ID NO: 2 of document D1 (human LERK-5) are identical. This document discloses chimeric polypeptides comprising the LERK-5 polypeptide and the "*Fc region of antibod*y". In a preferred and exemplified embodiment the Fc region is derived from IgG1 (cf. page 13, lines 3 to 35, pages 22 and 23, Examples 2 and 3 and claim 21). Document D1 also refers to LERK-5 polypeptide fusions with "*antigenic identification peptides*", i.e. epitope tag polypeptides (cf. *inter alia* page 8, lines 26 to 34). Moreover, document D1 refers to monoclonal antibodies directed against the LERK-5 protein and in Example 6 their production by hybridoma cells is exemplified (cf. page 2, lines 31-32, page 3, lines 10-12, page 27, Example 6 and claims 19-20).

12. Appellant's objection against claim 17 of the auxiliary request allowed by the opposition division was directed to the embodiment of a particular "*hybrid antibody*" which has now been deleted in the respondent's replacement main request and therefore, does not apply anymore. None of the alternative features characterizing the monoclonal antibody of present claim 12 are mentioned in document D1 and thus, the requirements of Article 54(1) in connection with Article 54(3) EPC are considered to be fulfilled.

Article 100(a) EPC/Article 56 EPC

13. Documents D2 and D3, both identified as possible alternative closest prior art documents in appellant's grounds of appeal, disclose the nucleotide and the amino acid sequences of the human Htk receptor referred to in the patent-in-suit (HpTK5 receptor in document D2; Htk receptor in document D3) and identify it as a member of the EPH/ECK subfamily of transmembrane tyrosine kinases receptors. The identification, importance and possible uses of a ligand of this receptor are also mentioned in these documents.

14. Starting from any one of these documents as closest prior art, the technical problem to be solved is the provision of the Htk (HpTK5) ligand. It is not contested that the (mouse) Htk ligand disclosed in the patent-in-suit provides a solution to this problem. The appellant argues, however, that this solution was obvious in the light of documents D2 or D3 combined with the common general knowledge of a skilled person and/or in combination with the teachings of document D4 (cf. Section XI *supra*).

15. Document D4 identifies the B61 protein as a GPI membrane-anchored ligand of the EPH/ECK subfamily of receptors which is also present in cell culture supernatants (soluble form). The appellant refers to the presence of extracellular proteases capable of cleaving membrane-bound proteins and releasing a soluble form thereof and argues that there is no reason to believe that the method used in document D4 would not work in identifying the transmembrane Htk ligand of the patent-in-suit (cf. Section XI *supra*). Apart from this argument, no evidence has been provided to support appellant's belief, in particular, the existence of a soluble form of the Htk ligand and, more particularly, its presence in the cellular supernatant of any of the cells and tissues identified in document D3 as expressing the Htk receptor (cf. page 14216, Figures 4 and 5 of document D3). There is no evidence on file for the presence of a native soluble form of the Htk ligand. Accordingly, the opposition division considered that there is also no evidence that the method disclosed in document D4 for the identification of the B61 protein/ligand could also be used to identify the Htk ligand (cf. page 8, point 15.3 of the decision under appeal). The board does not see any reason to deviate from the conclusion arrived at by the opposition division in this respect.

16. Moreover, since no ligands for members of the EPH/ECK subfamily of receptors had been identified in the prior art (cf. page 14217, right-hand column, third paragraph of document D3), the board further considers that, in the absence of any pointer in this prior art and/or in the closest prior art documents identified above, there

was no reason for the skilled person to look at prior art documents concerned with the isolation of (receptor) ligands anchored to the cell surface by a transmembrane domain - as it is the case for the Htk ligand of the patent-in-suit. In the board's view, such a combination would require hindsight knowledge of the patent-in-suit, as argued by the respondent (cf. Section XII *supra*).

Adaptation of the description

17. With its letter of 18 October 2011, the respondent provided pages 3, 20, 23 and 25 of the description adapted to respondent's replacement main request (cf. Section VII *supra*). The board is satisfied that the description was amended in accordance with the requirements of the EPC.

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 with the order to maintain the patent on the basis of the following documents:

   – claims 1 to 13 of the replacement main request filed on 18 October 2011,
   – description: replacement pages 3, 20, 23 and 25 as filed on 18 October 2011; pages 4 to 5 and 21 as filed on 21 May 2008 and pages 2, 6 to 19, 22, 24 and 26 to 32 of the patent specification,
   – Figures 1A to 5B of the patent specification, and
   – Sequence Listing of the patent specification.

The Registrar: The Chairman:

A. Wolinski M. Wieser