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Case Number: T 1450/07 - 3.3.08

Application Number: 95921317.4

Publication Number: 0826041

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Transforming growth factor Alpha HII

Applicant:
HUMAN GENOME SCIENCES, INC.

Opponent:
-

Headword:
TGFα-HII/HUMAN GENOME SCIENCES

Relevant legal provisions:
EPC Art. 56, 57

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request - inventive step - (yes)"
"Industrial applicability - (yes)"

Decisions cited:
T 0898/05

Catchword:
-

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Case Number: T 1450/07 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 11 February 2009

Appellant: HUMAN GENOME SCIENCES, INC.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 21 March 2007 refusing European patent application No. 95921317.4 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent application No. 95921317.4 with the title "Transforming growth factor Alpha HII" filed as International application PCT/US 95/06386 was published under No. WO 96/36709. It was refused by the examining division in a decision dated 21 March 2007.

Claim 1 **as originally filed** read as follows:

"1. An isolated polynucleotide comprising a member selected from the group consisting of:

(a) a polynucleotide encoding the polypeptide as set forth in SEQ ID No:2;

(b) a polynucleotide encoding the polypeptide comprising amino acids 1 to 329 of SEQ ID No:2;

(c) a polynucleotide encoding the polypeptide comprising amino acids 1 to 264 of SEQ ID No:2;

(d) a polynucleotide encoding the polypeptide comprising amino acids 215 to 329 of SEQ ID No:2;

(e) a polynucleotide encoding the polypeptide comprising amino acids 215 to 264 of SEQ ID No:2; and

(f) a polynucleotide capable of hybridizing to and which is at least 70% identical to the polynucleotide of (a), (b), (c), (d) or (e); and

(h) a polynucleotide fragment of the polynucleotide of (a), (b), (c), (d), (e) or (f)."

II. The decision of the examining division was taken on the ground that the main and first auxiliary requests then on file did not meet the requirements of Article 56 EPC (lack of inventive step of embodiments (g) to (i) of claim 1 of both requests) nor those of Article 57 EPC (claim 1 as a whole in both requests).

Claim 1 of the said **main request** read as follows:

"1. A polynucleotide selected from the group consisting of

(a) polynucleotides encoding a polypeptide comprising the amino acid sequence from residues 1 to 374 as shown in Seq.ID No.2;
(b) polynucleotides encoding a polypeptide comprising the amino acid sequence from residues 46 to 374 as depicted in Seq.ID No.2;
(c) polynucleotides encoding a polypeptide comprising the amino acid sequence from residues 46 to 309 as depicted in Seq.ID No.2;
(d) polynucleotides encoding a polypeptide comprising the amino acid sequence of residues 260 to 374 as depicted in Seq.ID No.2;
(e) polynucleotides encoding a polypeptide comprising the amino acid sequence from residues 260 to 309 as depicted in Seq.ID No.2;
(f) polynucleotides having a portion of the coding sequence as shown in Seq.ID No.1 encoding a polypeptide as defined in any one of (a) to (e);
(g) polynucleotides encoding a fragment of a polypeptide encoded by a polynucleotide of any one of (a) to (f), wherein said fragment is a TGFα-HII polypeptide;
(h) polynucleotides comprising a nucleotide sequence which is at least 70% identical to a polynucleotide of any one of (a) to (f) and which encode a TGFα-HII polypeptide; and
(i) polynucleotides encoding a polypeptide comprising an amino acid sequence which is at least 70% identical

to the amino acid sequence of a polypeptide encoded by a polynucleotide of any one of (a) to (f) and which encode a TGFα-HII polypeptide;

or the complementary strand of such a polynucleotide."

Claim 1 of the first auxiliary request differed from claim 1 of the main request in that items (a) to (e) were amended so as to be identical to items (a) to (e) of claim 1 as originally filed.

III. The appellant (applicant) lodged an appeal against this decision and filed a statement setting out the grounds of appeal together with a new main request and an auxiliary request. With the statement of grounds, an amended page 6 and pages 48 and 49 as well as Figure 1B identical with the corresponding pages of the application as filed were submitted.

IV. The examining division did not rectify its decision and the case was remitted to the board of appeal (cf. Article 109(2) EPC).

V. On 23 July 2008, the board sent a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), making known its preliminary, non-binding opinion.

VI. On 9 January 2009, the appellant filed further submissions in answer to this communication together with a new main request (claims 1 to 19) to replace both requests on file.

Claim 17 thereof read as follows:

"17. A nucleic acid molecule which specifically hybridizes to a polynucleotide of anyone of claims 1 to 4."

VII. In a telephone conversation on 3 February 2009, the rapporteur informed the appellant that the board would accept patentability of the main request filed on 9 January 2009 if claim 17 was amended for clarity reasons to recite that the claimed nucleic acid molecule hybridized to the polynucleotide of any one of claims 1 to 4 "under stringent conditions" rather than "specifically hybridized to the polynucleotide of any one of claims 1 to 4".

VIII. On 5 February 2009, the appellant submitted a new main request which corresponded to the claim request filed on 9 January 2009 with an amended claim 17.

Claims 1 and 17 read as follows:

"1. A polynucleotide selected from the group consisting of

(a) polynucleotides encoding a polypeptide comprising the amino acid sequence as shown in Seq.ID No.2;
(b) polynucleotides encoding a polypeptide comprising the amino acid sequence from residues 1 to 329 as depicted in Seq.ID No.2;
(c) an allelic variant of the polynucleotide of (a) or (b);

or the complementary strand of such a polynucleotide.

17. A nucleic acid molecule which hybridizes under stringent conditions to a polynucleotide of any one of claims 1 to 4."

Claims 2 to 4 related to further features of the polynucleotide of claim 1 and claims 5 to 7 to a vector containing such polynucleotide or a host cell containing such vector. Claims 8 and 9 were directed to processes for producing a TGFα-HII polypeptide or the cells expressing it. Dependent claims 10 and 11 to 15 respectively related to a TGFα-HII polypeptide and antibodies there against. Claim 16 related to an antibody against the polypeptide of claim 10 or to an antisense construct hybridizing to the polynucleotide of claims 1 to 4. Claims 18 and 19 related to pharmaceutical or diagnostic compositions comprising either one of the previously claimed compounds/host cells.

The request for oral proceedings was withdrawn.

IX. The following documents are mentioned in the present decision:

(3) : Derynck, R. et al., Cell, Vol.38, pages 287 to 297, August 1984;

(4) : Horie, M. et al., Genomics, Vol.67, pages 146 to 152, 2000;

(15) : WO 02/16429 published on 28 February 2002;

(20) : Afar, D.E.H. et al., Molecular Cancer Therapeutics, Vol.3, No.8, pages 921 to 932, August 2004.

X. The appellant's arguments in writing insofar as relevant to the present decision may be summarized as follows:

Articles 123(2) and 84 EPC

The embodiment (c) of claim 1 found a basis e.g. on page 7, last paragraph, of the application as filed. All claims which had been objected to for lack of clarity in the board's communication pursuant to Article 15(1) RPBA had been either deleted or amended in answer to the objections. The requirements of Articles 123(2) and 84 EPC were fulfilled.

Articles 56 and 57 EPC

- The identity of the claimed TGFα-HII *polypeptide*

The TGFα-HII polypeptide encoded by the polynucleotide of claim 1 comprised the six cysteine residues characteristic of the EGF/TGFα family members.
For homologies amongst growth factors of the EGF/TGFα family, the prior art described values of, e.g., 33% (between rat and mouse TGFα and mouse EGF) and sequence similarities such as 50% between the carboxy-terminal domain of betacellulin and rat TGFα. In view of this, the sequence identity of 26% and the similarity of 46% of TGFα-HII with human TGFα was well within the range a skilled person would expect between two EGF/TGFα family members.

Thus, the technical information contained in the application was sufficient for a person skilled in the art to immediately recognize that the now claimed polynucleotides encoded novel growth factors of the EGF/TGFα family.

- Article 56 EPC; inventive step

The closest prior art was document (3) concerned with the cloning of the human TNFα encoding DNA and its expression. In view of the disclosure therein that the total human genomic DNA did not contain additional TGFα sequences homologous to the one which it described, the isolation from the human genome of the polynucleotide of claim 1 encoding a further polypeptide belonging to the TNFα family was fully unexpected and inventive step should be acknowledged.

- Article 57 EPC; industrial applicability

The facts of this case were clearly in line with the principles established in the earlier case T 898/05 of 7 July 2006 that industrial applicability is acceptable if the disclosure in the application as filed on the function of a claimed compound (i) is plausible to the skilled person, (ii) is later confirmed by post-published evidence, and (iii) provides a clear basis for an industrial application. As already above mentioned, the structural features of TNFα-H2 left no doubt that it belonged to the EGF/TGFα family. Furthermore, there existed post-published evidence that TGFα-HII was over-expressed in prostate cancer and that anti-TGFα-HII antibodies conjugated to a cytotoxic agent showed sustained tumor growth inhibition (documents (15) and (20)). As for post-published document (4), it disclosed that TGFα-HII (identified as

TMEFF2) held promise as a candidate for use in the treatment of neurodegenerative disorders.
Thus, the above mentioned conditions (i) and (ii) were fulfilled and, besides, the TGFα-HII functions provided a clear basis for industrial application, namely in the field of pharmaceutical industry (condition iii)).
Therefore, the requirements of Article 57 EPC were fulfilled.

XI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claim request filed on 5 February 2009.

Reasons for the decision

Articles 123(2) and 84 EPC; added subject-matter and clarity

1. Claim 1(a) and (b) corresponds to claim 1(a) and (b) as originally filed (I, supra). Claim 1(c) finds a basis in particular on page 7, last paragraph of the application as filed. The amendment in claim 17 that the nucleic acid hybridizes under stringent conditions to a polynucleotide of any one of claims 1 to 4 finds a basis on page 10 of said application.

2. The objections for lack of clarity raised in the board's communication under Article 15(1) RPBA have all been taken care of by either deleting the offending claims or carrying out the necessary amendments.

3. The requirements of Articles 123(2) and 84 EPC are fulfilled.

Article 56 EPC; inventive step

4. The examining division acknowledged inventive step in relation to the TGFα-HII encoding polynucleotide as is now the subject-matter of claim 1 (a) and (b). The reason then given was that the closest prior art - document (3) disclosing human TGFα - taught on page 291, left-hand column that the human genome did not contain any additional sequences homologous to the TGFα gene and, therefore, that the isolation of the presently claimed polynucleotide homologous to the TGFα coding sequence was unexpected. The board agrees with this reasoning which equally applies to claim 1(c) which relates to allelic variants of the polynucleotide of claim 1(a) or 1(b), as well as to all other claims as they directly or indirectly relate to the TGFα-HII polypeptide/polynucleotide. Inventive step may, thus, be acknowledged to the claim request as a whole.

Article 57 EPC; industrial applicability

5. The existing case law establishes the criteria to be fulfilled for industrial applicability to be acknowledged (see eg. T 898/05 of 7 July 2006). The information in the application as filed should make plausible the identity of the claimed compound. Thus, the compound may be attributed to a known family of molecules on the basis of a comparison between its primary structure and that of molecules known in the art. Then, its putative functions must be disclosed. Experimental evidence is not necessarily needed. A number of reasonable assumptions may be made by taking into account the known functions of other family members as well as, for example and not exclusively, by

taking into account the distribution of the claimed compound in the body. It should also be clear that the treatments therein mentioned are in relation to the function plausibly attributed to the molecule. Post-published evidence backing up these assumptions is always welcome. In fact, the more information, the better and the quality of the information is also fundamental. As often repeated, each case must be evaluated on its own merit.

6. The present application identifies TGFα-HII as a member of the EGF/TGF family of transforming growth factors on the basis that it comprises a domain with six cysteine residues characteristic of that family and exhibits a degree of identity of 26% and a degree of similarity of 46% with the first isolated TGFα molecule - over a 236 amino acid stretch; see page 6, lines 14 to 18 of the application as filed. These are the features previously used in the art as characterizing features of EGF/TGF family members even if the percentages of homology, 33% in case of mouse, rat TGF and murine EGF (document (3), page 287), or of similarity, 50% between betacellulin and rat TGFα (application as filed, page 2) are somewhat different. In the board's judgment, this comparison makes it plausible that TGFα-HII is indeed a member of the EGF/TGF family.

7. As regards the properties of TGFα-HII itself, it is mentioned on page 6, lines 7 to 9, that:

"A polynucleotide encoding a polypeptide of the present invention may be obtained from human brain and early stage brain tissue."

Its putative functions and the therapeutic benefits to be drawn therefrom have been defined essentially as those earlier established for members of the EGF/TGF family. For example, it is mentioned on pages 20 and 21 that:

"There appears to be a widespread distribution of TGFα in various regions of the brain ... Accordingly, in instances where neurological functioning is diminished, an administration of the polypeptide of the present invention may stimulate the brain and enhance proper physiological function." and,

"TGFα-HII or soluble form thereof may also be employed to treat ocular disorders, for example, corneal inflammation. A variety of experiments have implicated members of the TGFα gene family in such pathologies." and,

"Treatment may also be related to liver regeneration or liver disfunction, since TGFα and its homologs and hepatocyte growth factor trigger hepatocyte regeneration after partial hepatectomy and after acute cell liver necrosis...".

8. Several post-published documents have been cited which experimentally confirm the information provided by the patent application. Document (15), Example 1 shows that a protein with the same sequence as TGFα-HII, namely TAT137 is over-expressed in prostate cancer. In document (20) (Abstract), it is described that an anti-TGFα-HII (identified as TMEFF2) monoclonal antibody conjugated to the cytotoxic agent auristatin E was used

with success to treat immunodeficient mice bearing xenografted prostate cancers.
Document (4) reports that TMEFF2 is widely expressed in the brain and that a fragment consisting of the extracellular domain of TMEFF2 increases survival of neurons. On page 152, the authors conclude that:

"These findings indicate that TMEFF2 holds promise as a candidate for use in the treatment of neurodegenerative disorders such as Parkinson's disease."

9. There is no doubt that the properties attributed to TGFα-HII make it suitable for use in the pharmaceutical industry.

10. In accordance with the above mentioned case law and taking into account the sum total of this information, it is decided that the requirement of industrial applicability is fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of claims 1 to 19 as filed on 5 February 2009 and a description and figures to be adapted thereto.

The Registrar The Chairman

A. Wolinski L. Galligani