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**Datasheet for the decision
of 15 January 2008**

Case Number: T 1127/05 - 3.3.04

Application Number: 97928698.6

Publication Number: 0951295

IPC: A61K 38/48

Language of the proceedings: EN

Title of invention:

Methods and compositions useful for inhibition of angiogenesis

Applicant:

THE SCRIPPS RESEARCH INSTITUTE

Headword:

Inhibition of angiogenesis/SCRIPPS RESEARCH INSTITUTE

Relevant legal provisions:

EPC Art. 54(1), (2), (5), 111(1), 123(2)

Act Revising the EPC Article 7.

Decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act Revising the EPC

CA/PL3/01 Rev.1

Relevant legal provisions (EPC 1973):

EPC Art. 97(2)

EPC R. 51(11)

Keyword:

"Article 54(2) EPC applies to the application"

"Added matter (no)"

"Novelty (yes)"

"Remittal (yes)"

Decisions cited:

G 0005/83, T 0254/93

Catchword:

see points 1 to 8



Case Number: T 1127/05 - 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 15 January 2008

Appellant: THE SCRIPPS RESEARCH INSTITUTE
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CA 92037 (US)

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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 31 March 2005
refusing European patent application
No. 97928698.6 pursuant to Article 97(1)
EPC 1973.

Composition of the Board:

Chair: U. Kinkeldey
Members: B. Claes
D. S. Rogers

Summary of Facts and Submissions

- I. European patent application No. 97928698.6, filed on 30 May 1997 as PCT/US97/09158 and published as WO 97/45137, was refused under Article 97(1) EPC 1973 by a decision of the examining division. The application has the title "Methods and compositions for inhibition of angiogenesis" and claims priority of US60/018,733 and US60/015,869, both published on 31 May 1996.

Claim 29 of the application as originally filed read:

"29. A method of inhibiting solid tumor tissue growth undergoing neovascularization in a patient comprising administering to said patient a composition comprising a therapeutically effective amount of an integrin $\alpha_v\beta_3$ antagonist sufficient to inhibit solid tumor tissue growth."

- II. The decision of the examining division was based on claims 1 to 25 filed with letter dated 30 January 2004.

Claim 1 read:

"1. The use of an $\alpha_v\beta_3$ antagonist in the manufacture of a medicament for inhibiting angiogenesis in a tissue by antagonism of $\alpha_v\beta_3$ receptors in said tissue, wherein said antagonist is an organic mimetic compound having a structure according to formula 7, 9, 10, 12 or 14."

Claims 2 to 25 related to specific elaborations of the use according to claim 1.

III. The following documents are referred to in this decision:

(1) Friedlander *et al.* (1995), *Science*, Vol. 270, pages 1500-1502.

(2) WO 97/06791 published on 27 February 1997.

IV. The decision of the examining division was solely based on the finding that the subject-matter of claim 1 before them lacked novelty over the disclosure in document (2), which was contained in the prior art by virtue of a lack of entitlement of the claim to the priority date. Document (2) disclosed the same organic compounds as recited in the claim, i.e. of formula 7, 9, 10, 12 and 14 and their use as $\alpha_v\beta_5$ antagonists for inhibiting ($\alpha_v\beta_5$ -mediated) angiogenesis. The present application disclosed that the same compounds were also inhibitors of $\alpha_v\beta_3$ and could provide ($\alpha_v\beta_3$ -mediated) inhibition of angiogenesis. The use of the compounds in the treatment of angiogenesis had thus been known in the prior art and the mechanism by which said angiogenesis was inhibited, either by $\alpha_v\beta_3$ or $\alpha_v\beta_5$ receptors, could not confer novelty to the claimed medical application in view of decision G 2/88 of the Enlarged Board of Appeal (OJ EPO 1990, 93, point 7.1) and T 254/93 of 14 May 1997 (point 4.8).

V. The appellant (applicant) lodged an appeal against this decision. With letter dated 11 December 2007, the applicant filed an auxiliary request comprising claims 1 to 24.

Claims 1 and 3 of the auxiliary request read:

"1. An $\alpha_v\beta_3$ antagonist for inhibiting $\alpha_v\beta_3$ -mediated angiogenesis in a tissue, wherein said antagonist is an organic mimetic compound having a structure according to formula 7, 9, 10, 12 or 14."

"3. An $\alpha_v\beta_3$ antagonist as claimed in claim 1, wherein said tissue is a solid tumor undergoing neovascularization, and said antagonist is for inhibiting the growth of said tumor tissue.

Claims 2 and 4 to 24 were dependent on claim 1.

- VI. In a communication pursuant to Article 17(2) of the Rules of Procedure of the Boards of Appeal the board drew the applicant's attention to Article 7 of the Act Revising the EPC of 29 November 2000, "Transitional provisions", and the Decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act Revising the EPC of 29 November 2000 (see special edition No. 1 OJ EPO 2007, pages 196 and 197, respectively).
- VII. Oral proceedings took place on 15 January 2008. The appellant requested that the decision under appeal be set aside and that a patent be granted based on claims 1 to 24 filed with letter dated 11 December 2007 (then auxiliary request), now the Main Request.
- VIII. The appellant's submissions presented in writing and during oral proceedings can be summarised as follows:

Claim format - First or Second Medical Use

- The Decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act Revising the EPC of 29 November 2000 provided in its Article 1.3 that Article 54(5) EPC shall apply to European patent applications pending at the time of its entry into force, in so far as a decision on the grant of the patent has not yet been taken. A refusal of the application pursuant to Article 97(1) EPC 1973 was not a decision on the grant of a patent. Moreover, even if it was then the fact that the decision had been appealed provided for a suspensive effect of this decision.

Amendments

- Basis for the amendment of claim 1 to recite inhibiting $\alpha_v\beta_3$ -mediated angiogenesis in a tissue could be found on page 110 of the application as filed.
- Basis for the amendment in claim 3 that the claimed antagonist is for inhibiting the growth of the solid tumor was provided by the wording of claim 29 as originally filed.

Novelty

- Document (2) was contained in the prior art pursuant to Article 54(2) EPC.

- What was claimed was the use of particular organic compounds for inhibiting $\alpha_v\beta_3$ -mediated angiogenesis in a tissue rather than angiogenesis in general or for inhibiting $\alpha_v\beta_5$ -mediated angiogenesis as disclosed in document (2).

- Document (2) did not disclose that the respective compounds were $\alpha_v\beta_3$ antagonists or the use of the compounds for the inhibition of $\alpha_v\beta_3$ -mediated angiogenesis but rather that they are $\alpha_v\beta_5$ specific antagonists (see page 8, lines 15 to 16 and 20 to 24) and their use for the inhibition of $\alpha_v\beta_5$ -mediated angiogenesis. $\alpha_v\beta_3$ -mediated angiogenesis was a different pathway from $\alpha_v\beta_5$ -mediated angiogenesis; it was mediated by different integrins and could be induced by different "angiogenic molecules" or cytokines, bFGF and VEGF, respectively.

- Admittedly, the claimed compounds could block both angiogenesis pathways in the same tissue and this was even inherently disclosed in document (2). However, as could be taken from document (1), there existed diseases, e.g. subretinal neovascular diseases such as age related macular degeneration, which have no association with VEGF, and thus $\alpha_v\beta_5$ -mediated angiogenesis.

- The discovery that angiogenesis could be inhibited by a different pathway of antagonism of $\alpha_v\beta_3$ receptors thus opened up new areas of therapeutic treatment. In the present case this was a specific new use of the known compounds in a method referred to in Article 53(c) EPC which was not

comprised in the state of the art, and was thus patentable, as provided for in Article 54(5) EPC.

Reasons for the Decision

Claim format - First or Second Medical Use

1. An issue in the present case is whether the EPC 1973 or EPC 2000 version of Article 54(5) applies to the European patent application in question.
2. Article 1, point 3 of the Decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act Revising the EPC of 29 November 2000 ("Transitional Decision") states:

"Article 54(5) [of EPC 2000] shall apply to European patent applications pending at the time of its entry into force, in so far as a decision on the grant of the patent has not yet been taken".
3. The decision of the Examining Division was to refuse to grant a patent. From Article 106 EPC the effect of the appellant's appeal is to suspend this decision, thus the appellant's European patent application remains pending and is thus a "European patent application(s) pending at the time of its [the EPC 2000] entry into force" within the meaning of Article 1, point 3 of the Transitional Decision.
4. A question arises, however, as to the meaning of "...a decision on the grant of the patent..". In English this

has two meanings as a "decision on the grant" can be either a positive decision to grant the patent, or a negative decision to refuse to grant a patent. The French and German versions of Article 1, point 3 of the Transitional Decision are similarly ambiguous.

5. By referring to the *travaux préparatoires* of the Transitional Decision which are found in the document CA/PL 3/01 Rev. 1 of 4 May 2001, "Revisions of the EPC: transitional provisions", this ambiguity can be resolved. Point 9 of this document states:

"Article 1, point 3, of the draft decision [that is of what became Article 1, point 3 of the Transitional Decision (board's remark)] provides for the new Article 54(5) to be applied to pending applications in cases where the decision on the grant of the European patent (Article 97(2), Rule 51(11) EPC) has not yet been taken at the time of entry into force of the revised version. This prevents the new provision from being applied to proceedings which have already been concluded, while at the same time ensuring that pending applications, as well as later applications, can benefit from purpose-related substance protection for further medical uses".

6. Article 1, point 3 of the draft Transitional Decision that is annexed as part II of document CA/PL 3/01 Rev. 1 of 4 May 2001 is identical to Article 1, point 3 of the Transitional Decision except that the first words of the draft version read "Article 54(5) shall be applied also to European patent applications...", whereas the final version reads "Article 54(5) shall apply to European patent applications...". This does

not appear to be a material difference in what concerns the present discussion.

7. The above reference in document CA/PL 3/01 Rev. 1 of 4 May 2001 to "Article 97(2), Rule 51(11) EPC" is a reference to Article 97(2) and Rule 51(11) EPC 1973. This is clear from first, the wording surrounding this reference to the EPC which refers to a time prior to the entry into force of the EPC 2000, and second, from the fact that it is only in the EPC 1973 that Rule 51(11) exists.

The relevant text of Article 97(2) EPC 1973 is:

"If the Examining Division is of the opinion that the application and the invention to which it relates meet the requirements of this Convention, it shall decide to grant the European patent for the designated Contracting states..."

The text of Rule 51(11) EPC 1973 is:

"The decision to grant the European patent shall state which text of the European patent application forms the basis for the grant of the European patent".

Thus the "decision on grant" referred to in Article 1, point 3 of the Transitional Decision is clearly a decision to grant a patent.

8. In this case the decision of the examining division was to refuse to grant a patent, thus within the sense of Article 1, point 3 of the Transitional Decision, no decision on the grant of a patent has been taken and

thus Article 54(5) EPC applies to the present application.

Amendments

9. The board is satisfied that the amendment in claim 1 now reciting "inhibiting $\alpha_v\beta_3$ -mediated angiogenesis in a tissue" (emphasis added) derives from the application as a whole and in particular the passage at page 110 of the application as filed, lines 26 to 29 referring to inhibiting $\alpha_v\beta_3$ -mediated angiogenesis as described in example 11.
10. The amendment in claim 3, now stipulating that the claimed antagonist is for inhibiting the growth of the solid tumor, is based on the wording of claim 29 as originally filed (see section I).
11. Accordingly the amendments to the claims comply with the requirements of Article 123(2) EPC.

Novelty

12. The board agrees with the examining division and the appellant that document (2) is contained in the state of the art by virtue of the undisputed lack of entitlement of the patent application, insofar as it concerns the compounds of the Main Request, to the priority date.
13. Document (2) discloses that, under physiological conditions, angiogenesis - a process of tissue vascularisation that involves the growth of new developing blood vessels into a tissue, also known as

neo-vascularisation - "is highly regulated and has been shown to be activated by specific angiogenic cytokines such as basic fibroblast growth factor (bFGF) and tumor necrosis factor- α (TNF- α). As described by Brooks ..., monoclonal antibodies against $\alpha_v\beta_3$ have been shown to block both bFGF- and TNF- α induced angiogenesis in model systems including the CAM model described below. As described in examples 4-6, monoclonal antibodies against $\alpha_v\beta_5$ block a **separate pathway of angiogenesis**, specifically that induced by vascular endothelial growth factor (VEGF), transforming growth factor TGF- α and epidermal growth factor (EGF)." (page 47, line 26 to page 48, line 2; emphasis added). The document continues that "in the context of the present invention, two pathways of angiogenesis are defined by distinct integrins, $\alpha_v\beta_3$ and $\alpha_v\beta_5$ ". Accordingly, and this is also confirmed by document (1), two distinct pathways for angiogenesis were known in the prior art each mediated by different integrins. Specific monoclonal antibodies to either of the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ could inhibit $\alpha_v\beta_3$ - and $\alpha_v\beta_5$ -mediated angiogenesis, respectively.

Document (2) furthermore discloses various groups of $\alpha_v\beta_5$ antagonists which can act as inhibitors of $\alpha_v\beta_5$ -mediated angiogenesis, i.e. the previously referred to $\alpha_v\beta_5$ monoclonal antibodies, linear or cyclic peptides or proteins and organic molecules which are mimetics of the $\alpha_v\beta_5$ ligand, also referred to as an organic mimetic, all of which specifically interact with $\alpha_v\beta_5$ (see page 8, lines 13 to 24).

Example 10 of document (2) discloses the "Preparation of Organic Molecule $\alpha_v\beta_5$ Antagonists", which according to the title of the section on page 41, line 20 to

page 42, line 11 of the document are " $\alpha_v\beta_5$ -specific mimetics". The compounds disclosed as organic mimetic compounds 7, 9, 10, 12 or 14 are identical to the organic mimetic compound having a structure according to formula 7, 9, 10, 12 or 14 as claimed in claim 1.

14. It has not been contested by the appellant that document (2) discloses the organic mimetic compound having a structure according to formula 7, 9, 10, 12 or 14 as claimed in claim 1 and their use in inhibiting ($\alpha_v\beta_5$ -mediated) angiogenesis. Accordingly, the provision of Article 54(4) EPC, which stipulates that the provisions of its paragraphs (2) and (3) shall not exclude the patentability of any substance comprised in the state of the art, for use in a method referred to in Article 53(c) EPC, provided that its use for any such method is not comprised in the state of the art, can not provide novelty for the subject-matter of claim 1.

15. Article 54(5) EPC on the other hand provides that the provisions of Article 54(2) and (3) EPC shall not exclude the patentability of any substance referred to in Article 54(4) EPC **for any specific use** in a method referred to in Article 53(c) EPC, provided that such use is not comprised in the state of the art.

It therefore needs to be determined whether the use of known organic compounds in the inhibition of $\alpha_v\beta_3$ -mediated angiogenesis, as claimed, is such a specific use that was not comprised in the state of the art.

16. Document (2) does not disclose, either explicitly or implicitly, the use of the organic mimetics for the

inhibition of $\alpha_v\beta_3$ -mediated angiogenesis. The achievement of this technical effect is however a technical feature of claim 1.

17. Document (1) at page 1502 (left-hand column, first full paragraph) discloses that angiogenesis is a common pathological feature of most ocular diseases that cause catastrophic loss of vision and notes that although ischemia-associated retinal neovascular diseases such as proliferative diabetic retinopathy are associated with increased VEGF, nonischemic retinal neovascular diseases such as age related macular degeneration have no such clear association. Accordingly, the fact that VEGF-stimulated (i.e. $\alpha_v\beta_5$ -mediated) angiogenesis proceeded by an integrin-mediated angiogenic pathway distinct from that stimulated by FGF (i.e. $\alpha_v\beta_5$ -mediated) angiogenesis supports the inference that different pathogenetic mechanisms may operate in retinal and subretinal angiogenesis related diseases.
18. The board concludes from the above referred to disclosure in document (1) that $\alpha_v\beta_3$ - and $\alpha_v\beta_5$ -mediated angiogenesis are associated with different diseases. Accordingly, the inhibition of $\alpha_v\beta_3$ -mediated angiogenesis by the organic mimetic compound having a structure according to formula 7, 9, 10, 12 or 14 as claimed in claim 1 is a specific use as compared to their use in the inhibition of angiogenesis in general or the inhibition of $\alpha_v\beta_5$ -mediated angiogenesis which was not comprised in the state of the art.
19. The examining division has argued that the present application discloses that the claimed compounds, which were known to be $\alpha_v\beta_5$ antagonists, are also inhibitors

- of $\alpha_v\beta_3$ -mediated angiogenesis. Since the use of the compounds in the treatment of angiogenesis was thus known in the prior art, the mechanism by which said angiogenesis was inhibited, either by $\alpha_v\beta_3$ or $\alpha_v\beta_5$ receptors, (i.e. both from document (2)) could not confer novelty to the claimed medical application.
20. The board cannot concur with the finding of the examining division. Certain examples of document (2) refer in a general manner to the use of the " $\alpha_v\beta_5$ -specific mimetics" as claimed in various experiments modulating angiogenesis. Example 6.C and 6.D describe the use of the organic molecules in tumor-induced angiogenesis (see in particular page 64, lines 19 to 23 and page 65, lines 16 to 24). Example 8 discloses a SCID/human chimeric model involving solid human M21L human melanoma cell line tumors on human skin grafts on SCID mice. On page 68, lines 2 to 11, intraperitoneal use of the $\alpha_v\beta_5$ antagonist peptide 189 was reported to result in a significant reduction of the tumor volume. The claimed compounds were reported also to have been tested for their effectiveness as $\alpha_v\beta_5$ antagonist in the above model (page 68, lines 12 to 15). Example 9 discloses inhibition of angiogenesis in a murine retinal angiogenesis model by a $\alpha_v\beta_5$ antagonsist (cyclic peptide). Also here the assays were reported to have performed with the claimed compounds (page 70, lines 4 to 5).
21. The board notes that from document (2) itself it is not disclosed whether the process for the inhibition of angiogenesis, besides being $\alpha_v\beta_5$ -mediated, is also $\alpha_v\beta_3$ -mediated. The fact that the claimed compounds can block both angiogenesis pathways in the same tissue may

inherently be disclosed in document (2). However, the board refers to point 12 above, in which it was concluded that that $\alpha_v\beta_3$ - and $\alpha_v\beta_5$ -mediated angiogenesis are associated with different diseases. The claimed compounds in their application of $\alpha_v\beta_3$ -mediated angiogenesis inhibitors open up new areas of therapeutic treatment.

22. In view of the above considerations and in following principles established in the decision G 5/83 of the Enlarged Board of Appeal (OJ EPO, 1985, 4), the subject matter of claim 1 of the Main Request is novel (Article 54 EPC). Since the dependent claims concern specific embodiments falling within the scope of independent claim 1, the subject-matter of these claims is also novel.

Procedural point

23. The decision of the examining division was solely based on the finding that the subject-matter of claim 1 before them lacked novelty over the disclosure in document (2). In order not to deprive the appellant of the two instance procedure established under the EPC for the consideration of objections to the grant of a patent, the board considers it appropriate to exercise its discretion under Article 111(1) EPC by remitting the case to the first instance for further prosecution.

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 for further prosecution upon the basis of the Main Request.

The Registrar

The Chair

P. Cremona

U. Kinkeldey