Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 3 December 2013

Case Number: T 0583/11 - 3.3.10

Application Number: 01117863.9

Publication Number: 1155689

IPC: A61L31/10, A61L31/16

Language of the proceedings: EN

Title of invention:
Anti-angiogenic stents and methods of their preparation

Patent Proprietor:
Angiotech Pharmaceuticals, Inc.
THE UNIVERSITY OF BRITISH COLUMBIA

Opponent:
Terumo Kabushiki Kaisha

Headword:
Anti-angiogenic stents /Angiotech Pharmaceuticals

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
Novelty - main request (no)
Inventive step - auxiliary request (no)

Decisions cited:
T 0249/88, T 1053/93

Catchword:

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0583/11 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 3 December 2013

Appellant: (Patent Proprietor 1)	Angiotech Pharmaceuticals, Inc. Suite 2120 Oceanic Plaza, 1066 West Hastings Street Vancouver, British Columbia V6E 3X1 (CA)
Appellant: (Patent Proprietor 2)	THE UNIVERSITY OF BRITISH COLUMBIA IRC Building, Room 331, 2194 Health Sciences Mall Vancouver, British Columbia V6T 1Z3 (CA)
Representative:	Gowshall, Jonathan Vallance Forresters Skygarden Erika-Mann-Strasse 11 80636 München (DE)
Respondent: (Opponent)	Terumo Kabushiki Kaisha 44-1, Hatagaya 2-Chome Shibuya-ku Tokyo 151-0072 (JP)
Representative:	Oser, Andreas Prüfer & Partner GbR Patentanwälte Sohnckestrasse 12 81479 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 21 January 2011 revoking European patent No. 1155689 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman:	P. Gryczka
Members:	J.-C. Schmid
	C. Schmidt

Summary of Facts and Submissions

I. The Appellant (Proprietor of the patent) lodged an appeal against the decision of the Opposition Division revoking European patent No. 1 155 689, independent claim 13 thereof readings as follows:

"13. A stent coated with a substance which will absorb an anti-angiogenic factor or an anti-angiogenic composition comprising an anti-angiogenic factor and a polymer, the substance having absorbed thereinto the factor or composition."

II. In its notice of opposition the Respondent (opponent) requested revocation of the patent-in-suit in its entirety on the grounds of lack of novelty and inventive step (Article 100(a) EPC), of insufficient disclosure (Article 100(b)), and of extending the subject-matter of the patent in suit beyond the content of the application as filed (Article 100(c) EPC). *Inter alia* the following documents were cited.

(1) WO-A-92/11896,

(4) WO-A-93/11120 and

(10) W.R.M Hermans et al."Prevention of restenosis after percutaneous transluminal coronary angioplasty: The search for a "magic bullet"", Restenosis (1991), pages 171-187

The Opposition Division held that claim 13 as granted met the requirements of Article 76 (1) EPC. However, its subject-matter lacked novelty over inter alia document (1). This document (1) disclosed a stent coated with a hydrogel comprising an active agent such

as heparin. Heparin had to be regarded as an anti-angiogenic factor in the sense of the broad definition given in the patent-in-suit which described neither the experimental conditions of the assay for determining the functionality, nor to which extent the reduction of the blood vessel had to occur. Furthermore heparin was disclosed in the patent-in-suit as an anti-angiogenic agent. The Opposition Division rejected the then pending auxiliary request, since it did not meet the requirements of Article 76 (1) and 123(2) EPC, and, thus revoked the patent-in-suit.

III. At the oral proceedings before the Board, held on 3 December 2013, the Appellant withdrew the first auxiliary request and defended the maintenance of the patent in suit on the basis of the claim as granted (main request) and on the basis of the set of claims according to the second auxiliary request filed with the letter of 31 Mai 2011 (auxiliary request).

Claim 9 of the auxiliary request differs from claim 13 as granted in that "the factor is anti-angiogenic by the CAM assay, wherein the anti-angiogenic factor is Taxol or a derivative of Taxol".

IV. According to the Appellant claim 13 of the patent as granted did not encompass a coated stent comprising heparin. Heparin was listed by error in the patent-in-suit as a suitable anti-angiogenic agent, which according to the patent-in-suit, meant a molecule which acted to inhibit vascular growth as determined by a test, such as the CAM assay. However, according to the experimental data annexed to the declaration of declaration of Darius V. Panaligan filed with the letter dated 4 February 2008 (document (12)), heparin proved negative by the CAM assay as an anti-angiogenic

factor. Since heparin was not an anti-angiogenic factor, the subject-matter of claim 13 was novel over document (1). As regards claim 9 of auxiliary request 1, document (1) was the closest prior document to the invention. The technical problem underlying the patent-in-suit was the provision of an alternative stent that is able to treat restenosis. The proposed solution was the stent of claim 9 which comprised Taxol or a derivative thereof. Stents coated with Taxol to treat restenosis were commercial and had already been launched since 1995. It was therefore not necessary to provide experimental data proving that the technical problem had been solved by the claimed subject-matter. Document (4) only addressed conjugates of Taxol, which was an essential feature of this document. The skilled person would have found no guidance in this document that Taxol itself would be effective when coated on a stent. Furthermore, document (4) dealt with a systemic administration of drugs, whereas document (1) was concerned with stents which delivered the drug locally. Therefore the skilled man would not have combined the teaching of these two documents. Document (10), which was a review article in the field of restenosis also supported inventive step. From this document it was apparent that the treatment of restenosis was a difficult matter, Taxol was not even mentioned in the review. The Respondent's obviousness analysis was based on hindsight. It was not predictable that Taxol would be efficient to prevent restenosis when delivered from a coated stent. The subject-matter of claim 9 of the auxiliary request thus involved an inventive step.

V. According to the respondent heparin was not listed by error in the patent-in-suit. Claim 13 of the patent-in-suit required an anti-angiogenic agent in its broadest

meaning, without any reference to an assay for determining the anti-angiogenic activity. Furthermore, the CAM assays described in document (12) could not show that heparin was not an anti-angiogenic agent since they were carried out with an insufficient dosage of heparin. Furthermore the anti-angiogenic activity of heparin was reported in the last paragraph of example 2 of the patent-in-suit. The subject-matter of claim 13 lacked novelty with respect to document (1) which disclosed a stent coated with a hydrogel comprising heparin. The subject-matter of claim 9 of the auxiliary request extended beyond the content of the parent application and furthermore lacked clarity on account of the expression "or derivative of Taxol". The closest prior art document was document (1) which disclosed a coated stent comprising an proliferative agent, such as heparin, to treat restenosis. The patent-in-suit contained no experimental data proving that the solution proposed of the technical problem of providing a alternative stent able to treat restenosis, i.e. the coated stent comprising Taxol or a derivative thereof, was efficient to prevent restenosis. The solution proposed was obvious in the light of the prior art, since document (4) provided a list of compounds useful for the treatment of restenosis, the list included both heparin and Taxol. The subject-matter of claim 9 of the auxiliary request lacked therefore an inventive step.

VI. The Appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims as granted as granted (main request), or subsidiarily, on the basis of the claims according to the second auxiliary request filed with the letter dated 31 Mai 2011 (auxiliary request).

The Respondent requested that the appeal be dismissed.

VII. At the end of the oral proceedings the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Novelty: claim 13 as granted*

2.1 Claim 13 is directed to a coated stent comprising an anti-angiogenic factor. The appellant and the respondent had divergent view on whether or not heparin was an anti-angiogenic factor.

According to paragraph [0023] of the patent-in-suit, anti-angiogenic factors should be understood to include any molecule which acts to inhibit vascular growth and that a variety of methods may be readily utilized to determine the anti-angiogenic activity of a given factor, including for example, chick chorioallantoic membrane (CAM) assays (see page 5, line 49 to 52). Furthermore, paragraph [0032] of the patent-in-suit exemplifies some anti-angiogenic factors that can be used within the context of the invention, including heparin (see page 7, line 8).

However, according to the Appellant heparin was listed by error in the patent-in-suit and was actually not an anti-angiogenic factor in the context of the invention according to the patent-in-suit. In support of its argumentation, it provided data showing that heparin

was negative in chick Chorioallantoic Membrane (CAM) assays as an anti-angiogenic agent (see document (12)).

In these assays, which are similar to those described in example 2 of the patent-in-suit, a methylcellulose disk containing 1 µg or 10 µg of the compound was placed on a fertilized chick embryo and viewed after 40 hours. The CAM assay was judged to be positive if it was devoid of a capillary network and/or major blood vessels were disrupted in an area of 2 to 6 mm. The results provided in document (12) showed the CAMs treated with heparin at concentrations of 1 µg and 10 µg were negative.

In the CAM assays of example 12 methothrexate was also shown to provide negative responses, although according to the patent-in-suit, it is an anti-angiogenic factor (see page 7, line 6 of the patent-in-suit). Consequently, the assays described in document (12) cannot show that a drug has no anti-angiogenic activity at all, and therefore, cannot prove that heparin was cited by error in the patent-in-suit. The Board furthermore notices, that an anti-angiogenic activity of heparin is reported in example 2 of the patent-in-suit where it is indicated that heparin formed an avascular zone which became revascularized 60 hours after application (see paragraph [0126] on page 19). It can thus not be concluded on the basis of the CAM assays that heparin is not an anti-angiogenic factor.

In addition, claim 13 does require the anti-angiogenic factor must specifically provide positive responses in CAM assays, let alone in the CAMs assays carried out with concentrations as so low as 1 µg and 10 µg. As can be seen from table 2 of example 2 of the patent-in-suit the anti-angiogenic activity depends on the

concentration of the active agent. Thus, with Taxol, at a concentration of 1 µg, of 15 embryos evaluated only 6 were CAM positive, at 10 µg it was 16 of 21. Only at a concentration of 30 µg all CAMs were positive.

Consequently, the argument that heparin was cited by error as an anti-angiogenic factor in the patent-in-suit did not convince the Board. Accordingly, as correctly pointed out at page 7, line 8,of the patent in suit heparin has to be regarded as an anti-angiogenic agent in the context of the patent-in-suit.

2.2 Document (1) discloses a stent coated with a hydrogel gel having absorbed a drug, such as heparin (see page 2, line 34; page 17, lines 7 to 13). Heparin is an anti-angiogenic factor (see point 2 above). Hence document (1) discloses a stent having all the features required by claim 13. Thus, the subject-matter of claim 13 as granted lacks novelty with respect to document (1).

Auxiliary request: claim 9

3. Novelty

Claim 9 of this request is directed to a coated stent comprising an anti-angiogenic factor which is restricted to Taxol or a derivative thereof. The Respondent did not raise any objection with regard to novelty of the subject-matter of claim 9 of the auxiliary request. The Board on its own does not see any reason to take a different view. Hence it is unnecessary to go into more detail in this respect.

4. *Procedural matter*

Although inventive step was not dealt with by the opposition division, the Appellant requested the Board not to remit the case to the Opposition Division for consideration of inventive step. Pursuant to Article 111(1) EPC the Board may exercise any power within the competence of the first instance or remit the case to that department. Since the patent-in-suit was filed as a divisional application having a filing date of 1994, the Board concurs with the Appellant's view that a remittal would delay the opposition proceedings after the date of expiration of the patent-in-suit and thus would not be appropriate. Under these circumstances, the Board decided not to remit the case to the first instance for the assessment of inventive step.

In view of the negative outcome with respect to inventive step, a decision of the Board on the issues of extension of the subject-matter of this claim beyond the content of the parent application as filed (Articles 76(1), 100(c) EPC) and of clarity (Article 84 EPC) objected to by the respondent is unnecessary.

5. Inventive step.

5.1 Closest prior art.

The Board considers, in agreement with the parties that document (1) represents the closest prior art to the invention, and, hence takes it as the starting point in the assessment of inventive step.

This document relates to the delivery of drugs to the walls of body lumens (see page 1, lines 4 and 5) and is more particularly concerned with the aftermath of angioplasty , in particular with restenosis or closing

of the vessel (see page 1, lines 21 to 29). It discloses a coated stent comprising an anti-proliferative, drug such as heparin (see page 2, line 31 to 26).

5.2 Technical problem underlying the patent-in-suit

In view of this state of the art, the Appellant submitted that the technical problem underlying the application was the provision of an alternative stent that is able to treat restenosis.

5.3 Solution

As a solution to this problem the patent proposes the stent of claim 9 which is characterized by the choice of Taxol or a derivative thereof as the therapeutic agent.

5.4 Success

The Respondent contested that the stent of claim 9 was a solution to this technical problem since the patent-in-suit did not contain any experimental data in this respect.

However since Taxol is known for the treatment of restinosis (see paragraph 5.5 below), the Board is satisfied that it is credible that the stent of claim 9 containing Taxol is able to treat restenosis.

5.5 Obviousness

It remains to be decided whether or not the proposed solution to that objective technical problem, namely

the stent according to claim 9 of the auxiliary request, is obvious in view of the state of the art.

Document (1) discloses a coated stent impregnated with an antiproliferative agent for the prevention of restenosis (see point 2 above).

When looking for an alternative coated stent for treating restenosis, it is a matter of course that the person skilled in the art would consider prior art documents disclosing further antiproliferative agent for treating restenosis. Thus, the skilled person would be struck by document (4) which discloses on page 50, line 13 to 17 antiproliferative agents for the treatment of post-angioplasty restenosis, including Taxol and the derivatives thereof.

The Board concludes from the above that document (4) gives to the person skilled in the art a concrete hint as to how to solve the problem underlying the patent in suit as defined in point 5.2 above of providing an alternative stent that is able to treat restenosis, namely by replacing heparin with an other proliferative agent such as Taxol or a derivative thereof, thereby arriving at the solution proposed by the patent in suit, i.e. the stent of claim 9 of the auxiliary request.

5.6 For the following reasons, the Board is not convinced by the Appellant's submissions in support of the presence of inventive step.

The Appellant submitted that document (4) only addressed conjugates of Taxol, which was an essential feature of this document. Accordingly, the skilled person would not have found any pointer in that

document (4) to consider Taxol itself for coating the stent.

Notwithstanding the fact that claim 9 of the auxiliary request also embraces the conjugates of Taxol, which are derivatives of Taxol, document (4) makes plain that Taxol exhibit its bio-activity only upon release from the conjugate (see page 10, line 34 to page 11, line 4). Therefore, although document (4) discloses as an essential feature that the actives are prepared and administrated as conjugates, the disclosure of Taxol as an antiproliferative agent useful for the treatment of restenosis on page 50 of that document is made independently from its administration under the form of a conjugate.

The Appellant further argued that the skilled person would not have combined the teaching of a document (4) dealing with a systemic administration of a drug with document (1) disclosing a stent which delivered locally the drug.

However, the skilled person is already aware from document (1) that restenosis can be treated using a coated stent delivering locally an antiproleferative agent. To provide an alternative to the stent of document (1), it is sufficient for the skilled man to find out an alternative antiproliferative agent disclosed to be useful to treat restenosis. Document (4) comprises such specific disclosure on page 50, which disclosure is made independently from any mode of administration of the agent.

The Appellant also referred to document (10), which is a review article in the field of restenosis, to show that there was an unsatisfied need for a drug that

prevents restenosis in patients undergoing angioplasty. Taxol was even not mentioned in this document as a potential agent to prevent restenosis. This was in itself an indication that the claimed subject-mater involved an inventive step.

Notwithstanding the fact that document (10) was drafted in 1991, and thus this review article considered neither the disclosure of document (1) (publication date July 1992) nor that of document (4) (publication date June 1993), such considerations merely concern a secondary indicia in the assessment of inventive step and cannot substitute the assessment of inventive step vis-à-vis the state of the art on an objective basis following the "problem-solution-approach".

The Appellant furthermore argued that the Respondent's obviousness analysis was based on hindsight and that was not predictable that Taxol would be efficient to prevent restenosis when present in a coated stent.

However,in order to render a proposed solution obvious it is sufficient to establish that the skilled person would have followed the teaching of the prior art with a reasonable expectation of success (see decisions T 249/88, point 8 of the reasons; T 1053/93, point 5.14 of the reasons; neither published in OJ EPO). In the present case, the Board cannot agree with the Appellant's argument that due to some purported uncertainty about the predictability of success of a stent coated with Taxol the skilled person would not have contemplated Taxol, since document (4) makes plain that Taxol is an antiproliferative agent which can be used for the treatment of post-angioplasty restenosis.

5.7 For these reasons, the solution proposed by claim 9 of the auxiliary request to the problem underlying the patent-in-suit is obvious in the light of the prior art.

5.8 As a result, the Respondent's auxiliary request is not allowable for lack of inventive step pursuant to Article 56 EPC.

Order

For these reasons it is decided that:

The Appeal is dismissed.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated