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Datasheet for the decision of 27 September 2006

Case Number: T 0918/04 - 3.3.04

Application Number: 97919658.1

Publication Number: 0966971

IPC: A61K 45/00

Language of the proceedings: EN

Title of invention:
Cerebral stroke/cerebral edema preventive or remedy containing IL-8 binding inhibitor as active ingredient

Applicant:
Chugai Seiyaku

Opponent:
-

Headword:
IL-8 binding inhibitor/CHUGAI SEIYAKU

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0918/04 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 27 September 2006

Appellant: Chugai Seiyaku
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 16 January 2004 refusing European application No. 97919658.1 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: M. Wieser
Members: B. Claes
D. Rogers

Summary of Facts and Submissions

I. The appeal was lodged by the applicant (appellant) against the decision of the examining division whereby the European patent application No. 97 919 658.1 was refused pursuant to Article 97(1) EPC. The European application was filed as international application PCT/JP97/01406 and published in English as EP 0 966 971 A1. The refusal was based on the finding that the subject-matter of the claims on file did not involve an inventive step within the meaning of Article 56 EPC.

II. In the statement setting out the grounds of appeal, the appellant requested to set aside the decision of the examining division and maintained the claim request on the basis of which the application had been refused, i.e. the "main submission" as filed with letter dated 4 November 2003. The appellant further requested oral proceedings pursuant to Article 116 EPC, in the event that the board did not intend to allow this "main submission".

III. Claim 1 of the "main submission" read:

"1. Use of an IL-8 binding-inhibition agent for the manufacture of a medicament for systemical administration for preventing or treating a cerebral condition selected from cerebral stroke, cerebral edema, cerebral ischemia, and increased cerebral vascular permeability."

IV. Following on from the statement of the grounds of appeal, the appellant filed in a further submission an English translation of Japanese document (3) (see section VIII) cited by the examining division.

V. In a communication pursuant to Article 12 of the Rules of Procedure of the Boards of Appeal the board expressed its provisional opinion that the subject-matter of claim 1 of the "main submission" lacked inventive step. Subsequently, the appellant was summoned to oral proceedings.

VI. In reply to the board's communication, the appellant submitted further written arguments in support of inventive step.

VII. One day before the oral proceedings the appellant withdrew the request for oral proceedings and notified the board that the appellant would not be represented during the oral proceedings. Accordingly, oral proceedings were held on 27 September 2006 in the absence of the appellant.

VIII. The following documents are cited in the present decision:

(1) Sekido *et al.* (1993), Nature, Vol. 365, No. 6447, pages 655-657.

(2) WO95/23865 A

(3) Onodera *et al.* (1994), NIPPON RINSHO, Vol. 52, No. 11, pages 2995-2999.

(3') English translation of document (3).

IX. The arguments put forward by the appellant in writing may be summarised as follows:

– Document (3') taught the explicit dose-dependent application of anti-IL-1ß antibodies for attaining an alleviation of edema following cerebral ischemia/reperfusion injury by administration of an anti-IL-1β neutralising antibody at an ischemic site, but was far less definite in the discussion of IL-8 in view of the explicit warning in the document that in reporting on experimental results it made reference to **rat** cytokine-induced neutrophil chemoatractant (CINC) instead of to IL-8. Therefore, document (3) did not prompt the skilled person to implement the claimed invention but rather and on the contrary lead the skilled person to implement the treatment of cerebral ischemic / reperfusion injury by administration of anti-IL-1ß antibody and thus lead away from the claimed invention.

– The skilled person would not have considered the systemic administration of large molecules, such as antibodies, for the treatment of the reperfusion injuries of the brain because of the blood-brain barrier, rendering it not possible for these antibodies to enter the brain and brain cells.

X. The appellant requested in writing that the decision under appeal be set aside and that a patent be granted in the version of a description and claims 1 to 13 filed with letter dated 4 November 2003, "main submission".

Reasons for the Decision

1. The issue to be decided in this appeal is whether or not the subject-matter of claim 1 of the "main submission" involves an inventive step.

2. For assessing this issue, the boards of appeal consistently apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art. In accordance with established case law of the boards of appeal the closest prior art is generally a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common.

Closest prior art

3. The examining division in its decision under appeal, had selected document (1) as the closest prior art.

During the examination procedure, reference was only made to the English abstract of Japanese document (3), i.e. Onodera *et al*. During the present appeal proceedings, the applicant filed an English translation of the whole of document (3) with a letter of 4 June 2004. This translation is document (3').

Any reference to the text of document (3) in the following discussion is to the corresponding text passage in the English translation document (3').

Document (3) specifically deals with the implication of neutrophil infiltration into the ischemic brain in the pathogenesis of ischemia /reperfusion injury and new methods of treatment of the disease based on this teaching (see e.g. abstract and page 2 line 29 to page 3 line 7).

Document (1) on the other hand discloses the use of an anti-IL-8 antibody to prevent tissue reperfusion injury after ischemia, emphasising the treatment for reperfusion of ischemic rabbit lung tissue.

The board therefore considers that the emphasis in document (3) on the treatment of a *cerebral* ischemia condition, rather than the treatment of *lung* ischemic tissue, renders document (3) the closest prior art for the assessment of whether or not the subject-matter of claim 1, at least in the aspect of cerebral ischemia, involves an inventive step.

4. From section I of document (3) it is known that neutrophil tissue infiltration plays an important role in and is the primary cause for the pathology of cerebral ischemia / reperfusion injury (see in particular page 2, lines 2 to 6; page 3, lines 3 to 5 and the "Conclusion" section bridging pages 11 and 12). Furthermore, in the sentence bridging pages 2 and 3 document (3') states in the context of cerebral ischemia (see page 2, line 36 to page 3, line 3) that "*there is the possibility that a method capable of minimizing the tissue infiltration and activation of neutrophils during the acute phase following vascular injury may serve as a new method of treatment for ischemia/reperfusion injury.*", and in the sentence

bridging pages 11 and 12 that "*the involvement of neutrophils in reperfusion injury is not limited to a discussion of cerebral ischemia, but rather the development of a drug capable of safely and transiently inhibiting neutrophil function would most likely be able to be applied to vascular injuries affecting various organs.*".

5. The beginning of section II.1. of document (3) describes the involvement of IL-8 in the neutrophil, migration, activation and adhesion to endothelial cells (see page 6, lines 16 to 22) followed by a reference to the disclosure in document (1) stating that *"Inhibition of neutrophil infiltration and injury reduction effects have previously been reported following administration of anti-IL-8 monoclonal antibody in an ischemia/reperfusion injury model of the lung."*. The authors of document (3) then, at page 6, lines 25 to 28 state that "*Activation of neutrophils by IL-8 and the action of an adhesion promoting mechanism are similarly presumed in cerebral ischemia/reperfusion injury.*" (emphasis added by the board).

The technical problem

6. On the basis of the above analysis of the disclosure in document (3) the board considers the technical problem to be solved to be the provision of a compound for systemic administration for preventing or treating **cerebral ischemia**, i.e. one of the conditions recited in claim 1.

7. The board sees no reasons to doubt that the application solves the above problem by the use of an IL-8 binding-

inhibiting agent, such as e.g. the anti-IL-8 antibodies as known from documents (1) and (2).

Inventive step

8. Document (3) indicates that in the context of cerebral ischemia a method capable of minimizing the tissue infiltration and activation of neutrophils during the acute phase following vascular injury may serve as a (new) method of treatment for ischemia/reperfusion injury (see point 4 above). It therefore needs to be established whether or not the prior art renders the use of an IL-8 binding-inhibiting agent in such a method of treatment for cerebral ischemia/reperfusion injury obvious to a skilled person.

9. From point 5 above, it can be taken that document (3) itself reflects the general knowledge of the skilled person that IL-8 is involved in neutrophil migration, activation and adhesion to endothelial cells.

Furthermore, document (3) by reference to document (1), reports the successful inhibition of neutrophil infiltration and injury reduction effects obtained by systemic, i.e. intravenous administration of anti-IL-8 monoclonal antibodies, i.e. an IL-8 binding inhibiting agent in accordance with claim 1, in an ischemia/reperfusion injury model of the lung (see page 6 lines 21 to 25) and continues that activation of neutrophils by IL-8 and the action of an adhesion promoting mechanism are similarly presumed in cerebral ischemia / reperfusion injury (page 6 lines 25 to 28).

Accordingly, the board is satisfied that for the skilled person at the priority date of the present application, IL-8 was at least one key element in the pathology of cerebral ischemia /reperfusion injury.

10. The board judges therefore that, in view of the explicit implication of IL-8 in cerebral ischemia / reperfusion injury pathology and the successful therapeutic effects on ischemic lung tissue, and in order to solve the above formulated technical problem, the disclosure in document (3) renders it obvious to a skilled person to select the anti-IL-8 monoclonal antibodies as disclosed in document (1).

11. The appellant has argued that document (3) teaches the explicit dose-dependent application of anti-IL-1ß antibodies for the alleviation of edema following cerebral ischemia/reperfusion injury by intraventricular (i.e. local and therefore non-systemic) administration of an anti-IL-1β neutralising antibody at an ischemic site (see page 9, 15 to 36). According to the appellant, document (3) is far less definite in its discussion of IL-8 compared to its discussion of anti-IL-1ß antibodies. The appellant supports this argument by referring to document (3), page 7, lines 8 to 12, where it is stated that in the ischemic brain of a rat, the rat IL-8 levels "*increased remarkably after 3-6 hours prior to neutrophil infiltration of the brain, and were found to continue to demonstrate elevated values until the day after ischemia*". The appellant points out that document (3) explicitly warns that the reference is not to IL-8 as cloned from e.g. humans, but to the rat cytokine-induced neutrophil chemoatractant (CINC). The action of IL-8 (CINC) does

not completely conform to that of human IL-8 (see page 6 line 15 to page 7 line 8). Due to the fact that the teaching with reference to IL-1 was so clear and encouraging, and since the discussion of IL-8 was less definite, document (3) would not have prompted the skilled person to implement the claimed invention but would, to the contrary, lead the skilled person to implement the treatment of cerebral ischemic / reperfusion injury by administration of anti-IL-1ß antibody and thus lead away from it.

The board does not agree with the appellant's argument for the following reasons.

Firstly, document (3) at page 7, lines 12 to 14, states that "*IL-8 (CINC) is presumed to play an important role in neutrophil infiltration of the cerebral parenchyma.*" and at the same page lines 22 to 25 that "*... it is believed that IL-8 is released from vascular endothelial cells at the ischemic site where it then promotes migration and activation of neutrophils.*". The board considers these statements as a clear message to the skilled person of the actual involvement of IL-8 in the pathological migration of neutrophils upon reperfusion of cerebral ischemic tissue and therefore of the fact that IL-8 inactivation is a suitable starting point for preventing cerebral ischemia.

Secondly, the board notes that although the authors of document (3) express caution as to whether such results would also be obtained with human IL-8, the results obtained with the rat IL-8 (CINC) are a pointer to the present invention. The board considers in this context that in formulating the caveat concerning the rat IL-8

(CINC) results, the authors of document (3) merely followed the routinely cautious approach of a clinician when reporting on new scientific results obtained from an animal model, rather than stating a concrete and factual prejudice against the involvement of human IL-8 in cerebral ischemia / reperfusion injury.

Thirdly, the board considers in this context that the mere disclosure of one possible (and possibly non-inventive) route for the treatment of a condition in the prior art (here the anti-IL-1ß antibody) cannot prejudice the skilled person from formulating other possible and alternate, and equally non-inventive, routes for the treatment of the same condition (here the use of the anti IL-8 antibody).

12. The appellant has furthermore argued that, at the priority date, the skilled person would not have considered the systemic administration of large molecules, such as antibodies, for the treatment of the reperfusion injuries of the brain because of the blood-brain barrier, rendering it not possible for these antibodies to enter the brain and brain cells.

The board is not convinced by this argument. Document (3) discloses the involvement of IL-8 in the migration of neutrophils to the ischemic target site and their activation and infiltration of tissue during the acute phase following vascular injury. Therefore, rather the mechanism of the inhibition of the migration and tissue infiltration of the neutrophils from the vascular site into the brain tissue is what is addressed and not the crossing of the blood-brain barrier by the antibody. Indeed, neutrophil activation by IL-8 takes place in

the blood vessels rather than in the brain, as is confirmed by Figure 1 of document (3) depicting the mechanism of the neutrophil tissue infiltration hypothesis. Accordingly, inhibition of the activation of neutrophils by anti-IL-8 antibodies likewise takes place in the blood vessel rather than in tissues beyond the blood-brain barrier.

13. For the above reasons the prior art renders the use of an IL-8 binding-inhibiting agent in a method of treatment for cerebral ischemia/reperfusion injury obvious to a skilled person. The subject-matter of claim 1 therefore lacks an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

Registrar Chair

P. Cremona M. Wieser