BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

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

D E C I S I O N
of 8 April 2005

Case Number: T 0669/04 - 3.3.8

Application Number: 93915351.6

Publication Number: 0672151

IPC: C12N 15/57

Language of the proceedings: EN

Title of invention:
Inhibitors of CED-3 and related proteins

Applicant:
Massachusetts Institute of Technology

Opponent:
-

Headword:
CED-3 inhibitors/MIT

Relevant legal provisions:
EPC Art. 84, 83

Keyword:
"Main request - claims - support by description (no); undue burden (yes)"
"Auxiliary request -claims support by description (yes); undue burden (no)"

Decisions cited:
T 0892/94, T 0190/99, T 0609/02

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0669/04 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 8 April 2005

Appellant: MASSACHUSETTS INSTITUTE OF TECHNOLOGY
77 Massachusetts Avenue
Cambridge
MA 02139 (US)

Representative: Arends, Will
Lloyd Wise
Commonwealth House
1-19 New Oxford Street
London WC1A 1LW (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 19 December 2003 refusing European application No. 93915351.6 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
S. C. Perryman

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division dated 19 December 2003 whereby the European patent application No. 93 915 351.6 (published as WO 93/25694) with the title "Inhibitors of CED-3 and related proteins" was refused pursuant to Article 97(1) EPC. The decision under appeal was based on a set of claims 1 to 21 filed on 28 October 2002.

II. The appellant filed an appeal and submitted the statement of grounds of appeal with a new set of claims 1 to 13.

III. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal (RPBA) indicating its preliminary non-binding opinion.

IV. Submissions in reply to the board's communication were filed on 8 March 2005 with a main request, which was the same as the one filed with the statement of grounds of appeal, and auxiliary requests 1 to 5.

V. Oral proceedings took place on 8 April 2005. During the oral proceedings the appellant filed auxiliary requests 6 and 7. However, at the end of the oral proceedings, the appellant withdrew all auxiliary requests on file except for auxiliary request 7 which was maintained as the sole auxiliary request.

VI. Claim 1 of the **main request** read as follows:

"1. The use of an inhibitor of an interleukin-1β convertase (ICE)/CED-3 protein for the manufacture of a medicament for the treatment of a disease or condition selected from the group consisting of myocardial infarction, stroke, traumatic brain injury, a neural degenerative disease, hair loss, pathogenic infection and viral infection in a patient having said disease or condition."

Claims 2 to 13 concerned further embodiments of claim 1 relating to the specific disease or condition (claims 2 to 9), to the type of inhibitor (claims 10 to 12) and to the (human) patient (claim 13).

VII. Claim 1 of the **auxiliary request** read as follows:

"1. The use of an inhibitor of the protease activity of a human interleukin-1β convertase (ICE) protein for the manufacture of a medicament for the treatment of a disease or condition selected from the group consisting of myocardial infarction, stroke, traumatic brain injury, a neural degenerative disease, hair loss, pathogenic infection and viral infection in a patient having said disease or condition, wherein said inhibitor is a peptide aldehyde containing the amino acid sequence Tyr-Val-X-Asp, wherein X is selected from the group consisting of Ala, His, Gln, Lys, Phe, Cha and Asp; wherein said inhibitor is Ac-Tyr-Val-Ala-Asp-CHO; or wherein said inhibitor is the cowpox virus CrmA protein."

Claims 2 to 9 and 10 corresponded, respectively, to claims 2 to 9 and 13 of the main request.

VIII. The following document is cited in the present decision:

D18: N.A. Thornberry, British Med. Bulletin, 1996, Vol. 53(3), pages 478 to 490.

IX. The appellant's arguments in writing and during oral proceedings may be summarised as follows:

Main request
Articles 84 and 83 EPC

The present invention was based on three different findings, namely (i) the characterization of the nematode CED-3 gene and of the corresponding CED-3 protein, shown to be involved in apoptotic or programmed cell death, (ii) the structural relatedness between the CED-3 protein and the human interleukin-1β convertase (ICE), and (iii) the reduction of apoptotic cell death by inhibition of the CED-3 protein in an animal (nematode) system.

Based on the identified structural relatedness, the application defined an ICE/CED-3 family characterized by conserved structural features, in particular an overall amino acid identity of at least 28%, a QACRG pentapeptide sequence (including the active cysteine required for protease activity) and two autoproteolytic cleavage sites (cleaved to produce the active enzyme). These shared structural features were directly related to the cell death activity and were the basis for a common inhibition of the apoptotic activity of the

ICE/CED-3 family members. Post-published evidence had been provided showing a cell death activity akin to that of the CED-3 protein for the ICE and the use of ICE inhibitors, previously identified only as anti-inflammatory agents, for inhibiting cell death caused by ICE or by other members of the ICE/CED-3 family. This evidence also demonstrated that the term "ICE/CED-3 family" was well-known and accepted in the prior art, with a clear technical meaning.

Claim 1 of the main request referred to generic inhibitors which, although structurally not defined, were, however, clearly characterised by being limited to inhibitors specific for members of the ICE/CED-3 family, i.e. products inhibiting the activity of a CED-3 protein (cell death) or the activity of an ICE protein (protease activity). These ICE inhibitors, such as the structurally unrelated aldehyde-modified peptides and the *crmA* gene product shown in the application and known in the prior art for their ability to treat inflammation, could be used now in accordance with the present invention to inhibit cell death. A list of other structurally unrelated ICE inhibitors had also been provided as a support for the use of the generic term "inhibitor" in the claim.

According to the established case law, in particular the decision T 190/99 of 6 March 2001, the claims had to be properly construed with a mind willing to understand, i.e. the claims had to be interpreted in a technically sensible manner and taking into account the whole disclosure of the application. Thus, following this case law, the generic inhibitors of claim 1, although not structurally characterised, were clearly

understood as being inhibitors of a cell death activity caused by a member of the ICE/CED-3 family. This cell death activity could be easily assayed by the bioassays referred to in the application and used for obtaining the results of Table 2 (ced-3-lacZ fusions which prevented programmed cell death). These results also demonstrated the usefulness of this bioassay for detecting ICE inhibitors with no structural similarity and/or different mechanisms of inhibition. In fact, the actual mechanism of inhibition was irrelevant since Article 83 EPC only required to "*disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art*", i.e. "how" to carry out the invention, but not to disclose "why" the invention worked. In this respect, reference was made to decision T 892/94 (OJ EPO 2000, 1) which concerned a case with claims directed to the use of general inhibitors too.

Auxiliary request
Article 123(2) EPC and Article 84 in combination with Article 83 EPC

All claims of this request had a formal basis in the application as originally filed. The subject-matter of claim 1 referred to inhibitors that were both structurally and functionally characterised. Post-published evidence on file had also been provided showing a function of ICE, and the use of ICE inhibitors, in the diseases and/or conditions referred to in claim 1 of this request.

X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed on 8 March 2005 or of the auxiliary request submitted at oral proceedings on 8 April 2005.

Reasons for the Decision

Main request
Article 84 in combination with Article 83 EPC

1. The application discloses the structure (amino acid sequences) of the human interleukin-1β convertase (ICE) and of the nematode (*Caenorhabditis elegans*) CED-3 protein as well as the nucleotide sequence of the corresponding genes. The identification of conserved functionally important sequences, in particular (i) the region surrounding the active cysteine (pentapeptide QACRG), (ii) the presence of two autoproteolytic cleavage sites which, once cleaved, produced the active form of the protein, and (iii) an overall amino acid identity of at least 28%, is taken in the application as a basis for defining a "ICE/CED-3 family" which comprises the human ICE and the nematode CED-3 protein as specific members.

2. The application refers to the known activity of human ICE (pro-IL-1β activation) and discloses a role of the nematode CED-3 protein in (programmed or apoptotic) cell death. It further refers to known ICE inhibitors (peptide aldehydes, cowpox virus crmA gene) and identifies several CED-3 inhibitors. Based on the referred structural similarities, the application

proposes a cell death activity similar to CED-3 protein for the human ICE and a protease activity similar to ICE (cleavage the IL-1β precursor) for the nematode Ced-3 protein (cf. *inter alia* page 14, lines 1 to 3 and 26 to 28 of the application as published). Along the same line, it further suggests the use of known ICE inhibitors for inhibiting the activity of the CED-3 protein, i.e. apoptotic cell death, or else the use of CED-3 inhibitors for inhibiting the ICE protease activity and the associated inflammation (cf. *inter alia* page 21, lines 23 to 28). It is worth noting at this point that in the application as filed these suggestions are not supported by any experimental data.

3. Nevertheless, the application goes further and extends this generalisation to other members of the proposed ICE/CED-3 family for which it is said to be "*highly likely that ... (they) would exhibit cell death and/or protease activity*" (cf. *inter alia* page 17, lines 6 to 11). The conservation of the identified functional domains among the ICE/CED-3 family members or their encoded products is said to suggest "*not only that these genes have similar activities, but that they and their encoded products function via similar mechanisms*" and that "*agonists and antagonists which affect the function of conserved regions of one ced-3/ICE gene or encoded protein will similarly affect other genes or encoded proteins in the family*" (cf. page 21, lines 14 to 23).

4. Claim 1 of the main request relates in general to the use of inhibitors of an ICE/CED-3 protein for the manufacture of a medicament for the treatment of specific diseases or conditions characterized by cell

death (cf. *inter alia* page 9, lines 5 to 10, page 17, lines 28 to 34). Claim 1, however, does not refer to the specific activity to be inhibited nor to the chemical structure of the inhibitor used, i.e. there is no restriction on the activity to be inhibited nor on the type or class of inhibitors used. In other words, claim 1 fails to define - functionally and structurally - the inhibitors used (cf. section VI, *supra*). The absence of these features leads - for the reasons given hereinafter - to a lack of clarity in the sense of Article 84 EPC in combination with an insufficiency of disclosure under Article 83 EPC.

Functional characterization of the inhibitor of claim 1

5. In the light of the application as a whole, the activities of the ICE/CED-3 members are not strictly limited to the ones explicitly referred to in the description, i.e. a CED-3 cell death and/or ICE protease activity. In fact, the application itself states that "*other functions of ... ICE may be discovered. These may include new activities ...*" (cf. paragraph bridging pages 21 and 22). Similarly, the cell death activity of the CED-3 protein is said to "*be tested in bioassays using transgenic nematodes*" (cf. page 17, lines 20 to 21). However, these bioassays are far from being of easy interpretation and of providing a straightforward result, since the pathways of cell death *in vivo* might involve many genes and mechanisms and might be triggered and/or inhibited in a variety of different ways (cf. page 48, example 2 and point 10, *infra*).

6. Moreover, whereas on the basis of the identified conserved structural similarities, a similarity in the substrate and inhibitor specificities of the ICE/CED-3 family members is suggested (cf. *inter alia* page 8, lines 19 to 23, page 14, lines 23 to 28, page 21, lines 23 to 28 and page 30, lines 19 to 25), there is evidence on file showing that this is not always the case. Differences in the substrate and inhibitor specificities of the ICE and the CED-3 protein are referred to in document D18 (cited as expert opinion) (cf. pages 482 to 483), which attributes "*the distinct macromolecular specificities, and hence functions, of these enzymes*" to the "*profound differences in both the geometry and the chemical composition*" of their active centre subsites (cf. page 481, last paragraph). Thus, contrary to the assertion made in the application, an inhibitor of one member of the ICE/CED-3 family will not necessarily - or "*highly likely*" (as stated in the application) - inhibit all other members of this family. Therefore, it can not be excluded that a given product, while not inhibiting the ICE protease activity or the CED-3 cell death, might, however, inhibit an (unknown) activity of another (unknown) ICE/CED-3 family member.

7. It follows from the foregoing that neither the broadest interpretation of claim 1 (any inhibitor of any possible activity of any ICE/CED-3 family member) nor even the narrowest interpretation of this claim (an inhibitor of the ICE protein or of the CED-3 protein activity) provides a clear and unambiguous (functional) characterization of the inhibitor to be used.

Structural characterization of the inhibitor of claim 1

8. As stated in point 4 above, there is no structural limitation for the inhibitor referred to in claim 1. In spite of this, with reference to the established case law, and in particular to the decision T 190/99 of 6 March 2001, the appellant has argued that illogical interpretations should be ruled out and the claim be interpreted in a technically sensible manner, i.e. construed by a mind willing to understand (cf. section IX, *supra*). The said decision, however, also emphasizes in an explicit manner the importance of taking into account the whole disclosure of the application.

9. In the present case, the application does not limit itself to the specific exemplified ICE/CED-3 inhibitors such as the known peptide aldehydes or the crmA gene of cowpox virus, since it contemplates the use of other "*chemical analogs of these inhibitors*" and "*equivalents*" thereof (cf. page 30, lines 23 to 25 and page 31, lines 23 to 26).

10. Furthermore, the ICE/CED-3 inhibitors are not limited to those that inactivate an ICE/CED-3 protein by interacting with the ICE/CED-3 active site, because the prevention of the normal ICE/CED-3 activity by a protein acting "*in a dominant negative or antimorphic fashion*" is also contemplated as well as the (indirect) inhibition by interaction with other proteins that normally interact with an ICE/CED-3 protein (cf. page 26, line 32 to page 27, line 31). As these ICE/CED-3 inhibitors are to be identified and tested in bioassays for cell death activity (cf. page 27, line 32 to page 28, line 1), it is evident that according to

the description also inhibitors acting at very different levels (ICE/CED-3 gene transcription, translation, processing, etc.) are contemplated. Appendix A filed with appellant's submissions of 8 March 2005 comprises a Table showing indeed the broad nature and structure of several possible ICE inhibitors. Thus, the absence of a structural inhibitor limitation in claim 1, cannot be compensated by reference to the whole disclosure of the application.

11. The references to other case law, and in particular to the decision T 892/94 (*supra*), do not support appellant's case, since the inhibitors referred to in the claims underlying for example this latter decision were structurally defined (aromatic acid ester of a phenol or of an aromatic alcohol) and functionally characterized (water-soluble to impart an antimicrobial action and/or to lower the pH of liquid body-secretion to a level inhibiting micro-organisms growth). In fact, the present case is more similar to the situation underlying the decision T 609/02 of 27 October 2004, for which the disclosed *in vitro* tests could not be performed since the "protagonists" of the tests, i.e. the **structure** of the active ingredient proposed for the pharmaceutical composition, were not made available (cf. T 609/02, *supra*, point 10 of the Reasons). In the said case the board decided that the claimed subject-matter covered "*limitless and untried downstream developments in relation to yet to be demonstrated molecular mechanisms ... (and) it amounts to no more than an invitation to set up further research programs for which no guidance is forthcoming*" (cf. T 609/02, *supra*, point 11 of the Reasons).

Conclusions

12. In the absence of a reference to the specific activity of the "*interleukin-1β convertase (ICE)/CED-3 protein*" to be inhibited and, in the light of the different inhibitor specificities of the ICE/CED-3 family members in combination with the absence of a structural characterization of the inhibitors used, the scope of claim 1 is considered not to be clear. In the board's judgement, it is only with undue burden that it can be completely determined by the skilled person.

13. Thus, the main request does not satisfy the requirements of Article 84 EPC in combination with Article 83 EPC.

Auxiliary request
Article 123(2) EPC

14. Formal basis for the subject-matter claimed in this request is found in the description of the application as filed (cf. eg. pages 30 to 31 under the heading "ICE inhibitors as inhibitors of cell death"). The request is considered to fulfil the requirements of Article 123(2) EPC.

Article 84 EPC in combination with Article 83 EPC

15. On the one hand, the inhibitor referred to in claim 1 is now required to inhibit "*the protease activity of a human interleukin-1β convertase (ICE)*", which is a clear functional characterization to be tested using known enzymatic assay methods (cf. page 17, lines 11 to 12) and, on the other hand, the inhibitor is also

structurally characterized by being of a specific peptide aldehyde class or clearly defined as cowpox virus CrmA protein (cf. section VII, *supra*). There is also post-published evidence on file (cited as expert opinion) which, *prima facie*, demonstrates a possible role or function of the ICE protein - and therefore, a possible beneficial use of ICE inhibitors - in each of the diseases and/or conditions mentioned in claim 1 of this request.

16. Thus, the claimed subject-matter overcomes the objection raised above under Article 84 EPC in combination with Article 83 EPC for claim 1 of the main request (cf. point 4 *supra*) and this auxiliary request satisfies the requirements of Article 84 EPC in combination with Article 83 EPC.

Further prosecution

17. In order to give the party an opportunity to have its case considered by two instances, the board decides to use its power under Article 111(1) EPC to remit 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 on the basis of claims 1 to 10 of the auxiliary request submitted at oral proceedings on 8 April 2005.

The Registrar: The Chairman:

A. Wolinksi L. Galligani