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**D E C I S I O N**  
**of 22 March 2005**

**Case Number:** T 0889/02 - 3.3.4

**Application Number:** 90911526.3

**Publication Number:** 0483247

**IPC:** C07K 15/06

**Language of the proceedings:** EN

**Title of invention:**

Recombinantly produced human membrane cofactor protein (MCP)

**Applicant:**

WASHINGTON UNIVERSITY

**Opponent:**

-

**Headword:**

Membrane cofactor protein/WASHINGTON UNIVERSITY

**Relevant legal provisions:**

EPC Art. 56

**Keyword:**

"Main request, first auxiliary request - inventive step (no)"  
"Second auxiliary request - inventive step (yes)"

**Decisions cited:**

-

**Catchword:**

-



Case Number: T 0889/02 - 3.3.4

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.4  
of 22 March 2005

**Appellant:** WASHINGTON UNIVERSITY  
**Applicant:** 1 Brookings Drive  
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**Representative:** HOFFMANN EITLE  
Patent- und Rechtsanwälte  
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**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 6 March 2002  
refusing European application No. 90911526.3  
pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairwoman:** U. M. Kinkeldey  
**Members:** M. R. J. Wieser  
S. C. Perryman

## Summary of Facts and Submissions

I. The appeal was lodged by the Applicants (Appellants) against the decision of the Examining Division to refuse under Article 97(1) EPC the patent application EP 90 911 526.3, international publication number WO 91/02002. The patent application has the title: "Recombinantly produced human Membrane Cofactor Protein (MCP)".

II. The Examining Division decided that claim 1 of the main request before them had been amended in such a way that it contained subject-matter extending beyond the content of the application as filed and thus contravened the requirements of Article 123(2) EPC).

Moreover, the Examining Division decided not to allow auxiliary requests 1 to 3, filed by the Appellants at the oral proceedings, to enter into the proceedings under Rule 86(3) EPC, as the claims of these requests had been considered to be deficient at least for inventive step (Article 56 EPC) from the beginning of the written procedure (cf point (10) of the appealed decision).

III. The Board issued a communication on 25 May 2004.

Oral proceedings were held on 22 March 2005 during which an amended main request and three auxiliary requests were filed.

IV. The Appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request, or one of the first, second or

third auxiliary requests, all submitted at oral proceedings on 22 March 2005.

V. Claim 1 of the main request read:

"An isolated soluble polypeptide comprising a variant of membrane cofactor protein (MCP) for use as a medicine:

wherein said variant of MCP inactivates isolated C3b and isolated C4b;

comprises amino acids 1-251 of Figure 1, or amino acids 1-251 of Figure 1 wherein one or two amino acids are substituted, inserted or deleted; and

does not contain the hydrophobic region of MCP (amino acids 295-326 of Figure 1)."

Claim 1 of the first auxiliary referred to "[A]n isolated soluble variant of membrane cofactor protein (MCP) for use as a medicine", but was otherwise identical to claim 1 of the main request.

VI. Claim 1 of the second auxiliary request read:

"An isolated soluble variant of membrane cofactor protein (MCP) for use as a medicine, wherein said variant of MCP:

inactivates isolated C3b and isolated C4b; and

consists of amino acids 1-254 of Figure 1, or amino acids 1-254 of Figure 1 wherein one or two amino acids are substituted, inserted or deleted."

Dependent claim 2 of the second auxiliary request referred to a MCP variant consisting of amino acids 1-254 of Figure 1. Claim 3 referred to a pharmaceutical

composition comprising the MCP variant according to claims 1 to 2; claims 4 and 5 referred to the use of these variants for the manufacture of a medicament for treating specific diseases.

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

- (1) J. Exp. Med., vol.168, 1988, pages 181 to 194
- (2) Eur. J. Immunol., vol.18, 1988, pages 1289 to 1294
- (3) J. Immunol., vol.138, 1987, pages 3850 to 3855
- (4) Proc. Natl. Acad. Sci. USA, vol.82, 1985, pages 859 to 863
- (5) J. Exp. Med., vol.163, 1986, pages 837 to 855

VIII. The submissions made by the Appellants may be summarised as follows:

The MCP variants according to claim 1 of the main request and the first auxiliary request were not disclosed in the cited prior art documents.

Document (1), representing the closest state of the art, described the biological activity of MCP but did not explicitly disclose its use as a medicine. It could not be derived in an obvious way from the disclosure in document (1), either if taken alone or in combination with other state of the art, that a soluble variant of MCP missing the hydrophobic region had the biological

activity of the native protein and could be used as a medicine.

The claims of the second auxiliary request were restricted to the medical use of a soluble variant consisting of amino acids 1 to 254 of MCP, thus missing large parts of the sequence of the native protein shown in Figure 1. The skilled person, even when adopting a "try-and-see" attitude, had no reason to assume that a protein when truncated to such an extent retains its biological activity and can be used for a purpose which is not explicitly mentioned in the document representing the closest prior art.

### **Reasons for the Decision**

1. MCP was initially identified by iC3/C3b affinity chromatography and designated gp45-70 (document (4), abstract). The protein was partially purified from human mononuclear cell lines and shown to have a cofactor activity for inactivation of C3b and C4b. It was suggested that the protein plays a major role in preventing autologous complement activation at the level of the C3 convertases (document (5), summary). MCP is absent from erythrocytes, but present as membrane-bound protein on human T and B lymphocytes, granulocytes, monocytes, platelets, endothelial cells, epithelial cells and fibroblasts (document (2), abstract). On most of these cells it occurs in two forms of molecular weight 63 kd and 68 kd. The quantity of each of the two species expressed is under genetic control and involves a two allelic system (document (3), abstract).

2. Document (1) discloses cloning and sequencing of MCP cDNA (pages 182 to 183 and Figure 1). The document teaches that the full-length MCP protein consists of a 34-amino acid signal peptide and a 350-amino acid mature protein. It has, beginning at the NH<sub>2</sub> terminus, four repeat units of about 60 amino acids, followed by a region of 25 amino acids that are rich in serine and threonine, 17 amino acids of unknown significance, and a 23-amino acid transmembrane hydrophobic region followed by a 33-amino acid cytoplasmic tail. The MCP gene was localized to human chromosome 1 at the same bands that contain the multigene family of complement-regulatory proteins (document (1), summary on pages 190 to 191 and Figure 6). Control of the complement system is described as being essential to prevent damage to autologous tissue and MCP, because of its wide tissue distribution and cofactor activity, is proposed as an important membrane protein for protecting host cells from damage by complement (Document (1), page 181, first sentence and page 182, second full paragraph).

Document (1) does not refer to MCP variants and does not explicitly mention the use of MCP as medicine.

*Main Request and first auxiliary request*

3. Claim 1 of these requests refers to an isolated soluble variant of MCP, respectively to a polypeptide comprising it, for use in medicine. The variant **comprises** amino acids 1 to 251 of Figure 1 and does not contain the hydrophobic region of the native protein. Such a variant of MCP is not disclosed in the prior art

documents on file. Claim 1 of both requests is therefore novel (Article 54 EPC).

4. Document (1) (see point (2) above) is considered to represent the closest prior art.

The problem to be solved in the light of the disclosure in document (1) is seen in the actual provision of a medicament for protecting host cells from damage by complement.

5. The Appellants argue that the solution to this problem according to claim 1, namely the provision of a soluble MCP variant missing the hydrophobic region, is not obvious to the skilled person as it could not have been foreseen that the protein without amino acids 295 to 326 would retain its biological activity and inactivate isolated C3b and isolated C4b.
6. The present application describes on page 15, line 17 to page 16, line 4 the preparation of various forms of medicaments which make it possible to administer the active compound, MCP, to patients in need thereof by different ways. MCP is said to be generally formulated for injection, wherein the protein is dissolved in liquid, aqueous medium. Besides injection, MCP can be administered via suppository, oral or transmucosal administration, including sprays and by slow release formulations. Additional formulation techniques include encapsulation and conjugation to target directed ligands.



It belongs to the general knowledge of a person skilled in the field of preparing medicaments that pharmaceutical compositions can be prepared in a more convenient way by using soluble proteins devoid of hydrophobic regions, such as a transmembrane hydrophobic region of a protein which is responsible for anchoring the native protein to the cellular membrane.

7. Document (1) discloses the length and exact position of the transmembrane hydrophobic region of MCP. The Board, while accepting that by deleting this region it cannot be ruled out that the truncated protein will lose all or part of its original biological activity, nevertheless is of the opinion that a skilled person when trying to solve the problem underlying the present invention, namely the provision of a medicament, would try to solubilize MCP by deleting its transmembrane hydrophobic region.

In spite of the uncertainties which always characterise biological experiments, the skilled person had a reasonable expectation based on general experience that deletion of the hydrophobic region allowed solubility to be achieved without total loss of biological activity and was thus a worthwhile and easily practicable approach to making a soluble medicament, and the skilled person had no particular reasons in the case of MCP to expect failure. The skilled person would thus adopt the "try and see" attitude, and envisage this approach to solubilizing MCP.

For these reasons, claim 1 of both the main request and the first auxiliary request is found to lack an inventive step. Accordingly, these requests are not allowable under Article 56 EPC.

*Second auxiliary request*

8. Claims 1 to 5 of this request are based on claims 10 and 12; page 12, lines 23 to 28; example 5 and page 15, lines 2 to 16 of the application as originally filed (Article 123(2) EPC).

9. Claim 1 refers to an isolated soluble variant of MCP for use as a medicine **consisting** of amino acids 1 to 254 of Figure 1, or to variants thereof wherein one or two amino acids are substituted, inserted or deleted.

Such variants, pharmaceutical compositions containing them, or their use for the manufacture of a medicament are not disclosed in the prior art documents on file. Accordingly, claims 1 to 5 are novel and meet the requirements of Article 54 EPC.

10. Also for this claim document (1) is considered to represent the closest state of the art.

The problem to be solved is identical to the one formulated in point (4) above for the main- and the first auxiliary request, namely the provision of a medicament for protecting host cells from damage by complement.

11. The solution according to claim 1 is the use as a medicine of a variant of MCP consisting almost exclusively of the four short consensus repeats (SCRs) at the NH<sub>2</sub> terminus of the native protein (amino acids 1-251). As can be seen from the disclosure on page 9 of the application, this variant not only lacks the transmembrane hydrophobic region and the cytoplasmic tails of the native protein, but also almost the entire serine-threonine rich region (ST region, amino acids 252-280) and the sequence of unknown significance (UK region, amino acids 281-294).
  
12. While a skilled person trying to prepare a medicament containing an active variant of MCP has good reasons to delete the transmembrane hydrophobic region of the native protein (see point (6) above), the Board cannot identify an incentive that would encourage the expert to truncate the native protein for its use as medicine as required by claim 1.

Based on his/her knowledge that the biological activity of a protein, in the present case the ability of MCP to inactivate isolated C3b and C4b, is highly dependent on its secondary and tertiary structure, resulting from its primary structure, the amino acid sequence, and considering that the deletion of a single amino acid may have great influence on the three-dimensional folding of a protein or parts thereof, the expert has no reason to assume that such a drastically truncated protein would retain its desired biological activity. Checking on this would amount to embarking on research with quite uncertain outcome.

13. Document (1), which does not explicitly refer to the use of MCP as medicine or to pharmaceutical compositions containing it, does not contain information from which a skilled person could deduce that a MCP variant consisting only of the first 254 amino acids of the full-length protein retains the biological activity of the native protein and is able to inactivate isolated C3b and C4b.

The same holds true for all other prior art documents on file.

14. The Board comes to the conclusion that a skilled person trying to solve the underlying technical problem and to provide a medicament for protecting host cells from damage by complement, would not arrive at the subject-matter of claims 1 to 5 of the second auxiliary request in an obvious way.

Therefore, the claims involve an inventive step and meet the requirements of Article 56 EPC.

**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 5 of the second auxiliary request submitted at the oral proceedings on 22 March 2005 and a description yet to be adapted thereto.

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey