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D E C I S I O N
of 27 November 2001

Case Number: T 0747/98 - 3.3.4

Application Number: 87902905.6

Publication Number: 0261224

IPC: G01N 33/53

Language of the proceedings: EN

Title of invention:

Synthetic HTLV-III peptides, compositions and uses thereof

Patentee:

ORTHO PHARMACEUTICAL CORPORATION

Opponent:

Dade Behring Marburg GmbH
United Biomedical Corp.

Headword:

HTLV-III peptides/ORTHO

Relevant legal provisions:

EPC Art. 56

Keyword:

"Inventive step (yes)"

Decisions cited:

-

Catchword:

-



Case Number: T 0747/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 27 November 2001

Appellant:
(Opponent 01)

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Representative:

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Respondent:
(Proprietor of the patent)

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Decision under appeal:

**Interlocutory decision of the Opposition Division
of the European Patent Office posted 8 June 1998
concerning maintenance of the European patent
No. 0 261 224 in amended form.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey

Members: L. Galligani
V. Di Cerbo

Summary of Facts and Submissions

I. The appeal was lodged by opponents 01 against the interlocutory decision of the opposition division dated 8 June 1998 whereby the European patent No. 0 261 224, claiming priority from US 843 437 of 24 March 1986, was maintained on the basis of claims 1 to 17 of the first auxiliary request filed on 5 March 1998 and an amended description.

II. Claim 1 of the said request read as follows:

"A synthetic peptide having one of the following formulae:

[sequence of peptides (I), (III) to (VI), (VIII), (X), (XII) to (XIV) recited]."

Claim 2 was directed to the peptide of claim 1 in cyclic monomeric, dimeric or polymeric form. Claims 8 to 17 concerned methods or diagnostic kits in which use was made of a peptide of claim 1 or claim 2.

Independent claim 3 read as follows:

"A mixture of at least a first and a second peptide, wherein:

said mixture has enhanced recognition for antibodies to HTLV-III virus as compared to each peptide taken alone:

said first peptide is one of the following peptides

[sequence of peptides (I) to (III), (V), (VII) to (X), (XII) and (XIII) recited]

said second peptide is one of the following peptides

[sequence of peptides (IV) to (VI), (VIII), (XII),
(XIV) to (XV) recited]

or any one of those peptides in which the I residue in
the subsequence LLGIW has been substituted by a L, M
or F residue, provided that the first and second
peptides are different."

Claims 4 to 7 concerned particular embodiments of the
mixture of claim 3.

The opposition division decided that the said claims
complied with all the requirements of the EPC, in
particular that they involved an inventive step having
regard to the following documents:

(E6) Bio/Technology, Vol. 3, October 1985, pages 905
to 909;

(E9) Proc. Natl. Acad. Sci. USA, Vol. 83, August 1986,
pages 6159 to 6163.

The right to priority was acknowledged only for the
peptides (II) to (V). Thus, document (E9) constituted
prior art for all the remaining peptides.

III. In their statement of grounds of appeal, the appellants
disputed essentially the presence of an inventive step
having regard to document (E9) and to the following
further documents:

(E1) Nature, Vol. 313, 1985, pages 277 to 284;

(E5) Science, Vol. 229, 1985, pages 1402 to 1405;

(E8b) US-A-4 689 398.

In their view, the skilled person, who knew from documents (E5) and (E8b) the advantages of using synthetic peptides in the diagnosis of HTLV, would have investigated the gp41 region of HTLV-III shown to be suitable for diagnosis, in particular the region shown to be particularly advantageous by document (E6). Document (E1) had shown the correlation between HTLV-I and HTLV-III and had indicated in Figure 5 the presence of two closely located cysteine residues. Document (E8b) had drawn attention to the domain of amino acids 350 to 422 (three arrows) which, according to document (E1), corresponded to the domain 557 to 629 of HTLV-III. In view of all this knowledge, the skilled person would have synthesised overlapping peptides of this domain and tested their reactivity with serum. This was exactly what had been done in the patent in suit.

Moreover, document (E9) disclosed in Table 1 immunoreactive peptides which were structurally very close to those of claim 1. For example, peptide 11 of document (E9) differed from peptide XIV of claim 1 only in that the latter was extended by four amino acids. It was obvious for a skilled person to extend slightly a diagnostic peptide.

The appellants added as a final general remark that if inventive step was acknowledged, then there was a problem of sufficiency of disclosure, no specific arguments being put forward in respect of this allegation.

- IV. The respondents (patentees) filed observations on the statement of grounds of appeal.
- V. No submissions were received from opponents 02.
- VI. On 11 October 2001, following the summons to oral proceedings, the board issued a communication with an outline of the points to be discussed.
- VII. On 29 October 2001, the respondents filed an amended set of claims (main request) which differed from the claims as accepted by the opposition division in that an error in a sequence recited in the claims had been corrected. They also filed an auxiliary request.
- VIII. Oral proceedings took place on 27 November 2001. Both the appellants and opponents 02 (party as of right according to Article 107 EPC), who had already informed the board of their intention not to attend the hearing, were not represented.
- IX. The respondents essentially argued that in 1985 the nucleotide sequence of the HTLV-III virus had just been established (cf document (E1)) and there were hardly any data about the immunogenicity of the encoded proteins. There was nothing in support of the assumption made by the appellants that the diagnostically useful epitopes of HTLV-III would be exactly as those of HTLV-I. Although the usefulness of short peptides reacting possibly with all antisera was recognised, it was not known which HTLV-III peptides were immunogenic and how many epitopes were available. Peptides representing (a) useful epitope(s) could be located anywhere within the sequence of the viral proteins. The number of possibilities was huge.

Document (E6) had identified a diagnostically useful peptide of 82 amino acids as part of the gp41 protein. At best it could be said that the prior art (cf documents (E1), (E8b), (E6)) rendered an investigation within the gp41 region of HTLV-III "obvious to try", but only with hindsight it could be stated that the identification of the specific peptides of the claims was to be reasonably expected. As a matter of fact, document (E9) showed that the preparation of a number of overlapping peptides within a gp41 region encompassing 102 amino acids lead only to one peptide of 21 amino acids (peptide no. 8) that was reactive with HTLV-III antisera, the other peptides being weakly reactive. Of them, peptide no. 11 referred to by the appellants as being structurally close to one of the claimed peptides was shown to be diagnostically useless. Thus, document (E9) provided no incentive at all to investigate further peptides for which a diagnostic use was no feasible. Also document (E6) provided neither a motivation nor an incentive for truncating or fragmenting the 82 amino acid peptide which was disclosed as being highly immunogenic. Also the indication of the presence of two cysteine residues in the structure of the env-lor protein of HTLV-III as such was not indicative of any particular diagnostic usefulness of that domain. For these reasons, the appellants' reasoning was based on hindsight and failed to show that the claims at issue lacked an inventive step.

- X. The appellants requested in writing that the decision under appeal be set aside and the patent be revoked.

The respondents requested that the decision under appeal be set aside and that the patent be maintained

on the basis of claims 1 to 17 (main request) or claims 1 to 16 (auxiliary request) both filed on 29 October 2001, the expression "or claim 1" in claim 12, item a) of the main request being corrected in "of claim 1", and amended pages 4 to 8, 20 of the description as filed on 5 May 1998, and pages 3, 9 to 19 as granted.

Reasons for the Decision

1. The essential difference between the claim request accepted by the opposition division and the main request now on file is the correction of an error in the sequence of peptides (IV), (V), (XII) and (XV), namely the deletion of the additional Y residue (NB: Y is the standard one letter code for the amino acid tyrosine) which had mistakenly been incorporated during revision of the claim request before the opposition division. The said correction is obvious as it is immediately evident from the patent specification as granted as well as from the application as filed that nothing else was intended than what is offered as the correction because everywhere the sequences in question contain in that position only one Y residue. Thus, the correction is allowed under Rule 88 EPC.
2. The key issue here is that of inventive step, no specific arguments having being put forward by the appellants in respect of the issue of sufficiency.
3. In the board's judgement, the closest prior art is represented by document (E6) for the claimed embodiments entitled to the priority date (peptides II to V) and document (E9) for those entitled only to the

filing date (all other peptides). It should be noted that the finding on priority was not disputed by the respondents.

Both documents are concerned - as the patent in suit - with a peptide reactive with HTLV-III antisera. Document (E6) describes an antigenic peptide, designated peptide 121, containing 82 amino acids residues which represents a segment of the HTLV-III gp41 envelope protein. Document (E9) discloses a number of peptides with overlapping structures covering a region of 102 amino acids of gp41, of which only one (peptide no 8) is found to be highly reactive with sera from HTLV-III infected patients, the other ones showing much lower or hardly any reactivity (cf Table 1 on page 6161).

4. In the light of the said prior art, in both cases the problem to be solved is finding further suitable peptides.
5. As a solution the claims propose a number of specific peptides which correspond to residue sequences within the gp41 protein of HTLV-III, said peptides having in common either the sequence CSGKLIC or LLGIW (NB: here also the letters represent the standard one letter code for the amino acids). The said peptides are shown to be recognised by a number of HTLV-III antibody positive sera and to be particularly useful in a mixture of at least a peptide of the first class (common sequence CSGKLIC) with a peptide of the second class (common sequence LLGIW). Thus, the board is satisfied that the underlying technical problem is solved.
6. The relevant question is whether in order to solve the

underlying technical problem the skilled person would have readily selected within the known sequence of the gp41 protein of HTLV-III specific peptides having the specific sequences recited in the claims.

7. In the board's judgment, the answer to the above question is negative both for the embodiments entitled to the priority date and those entitled only to the filing date for the following reasons:

7.1 As regards the embodiments entitled to priority:

(a) Although the sequences of the claimed peptides are all comprised within the larger sequence of peptide 121 of document (E6), the latter does not provide any hints in the direction of selecting any particular peptide within the said sequence. On the one hand, the document is completely silent about any possibility of truncating or fragmenting peptide 121. On the other hand, even assuming - for the sake of reasoning - that the skilled person had some reasons for truncating or fragmenting the said peptide, he or she was not in a position to select, among the huge number of possible peptide fragments, the specific peptides of the claim and, in addition, to reasonably expect that they would retain their reactivity.

(b) Suggestions in that direction could also not be derived from any other of the documents cited. Of them: (i) Document (E1) describes the complete nucleotide sequence of HTLV-III together with the predicted amino acid sequence of the four largest open reading frames. It also describes schematically the structure of the env-lor product

and indicates the presence of two closely located cysteine residues. None of these data or indications constitute a useful hint for selecting any of the claimed peptides; (ii) Document (E8b) discloses synthetic peptides simulating hydrophilic envelope regions of HTLV that are structurally different from the ones claimed. No possible homology study (eg homology between HTLV-I and HTLV-III) would lead the skilled person to the peptides of the claims; (iii) Document (E5) relates to the general characterisation of the gp41 protein of HTLV-III and, as prior art, is further remote from the invention than document (E6).

- (c) Thus, there is no possible combination of documents that leads the skilled person in an obvious manner to the subject-matter of the claims.

7.2 As for the embodiments entitled to the filing date:

- (a) As already stated, for these embodiments document (E9) constitutes the most relevant prior art. Although this document uses an approach similar to that of the patent in suit in searching for suitable epitopes, its teaching focuses primarily on a particular peptide within the region investigated, namely peptide No. 8 which is found to be highly reactive. The remaining overlapping peptides are shown to be much less or hardly reactive (cf results reported in Table 1 on page 6161). These results would not encourage the skilled person to seek further structural changes in the direction of the claimed peptides.

(b) Nor are such structural changes suggested by any possible combination of the above teaching with that of any of the documents cited in point 7.1 above as none of them invites the skilled person to further investigate in the domain already investigated by document (9) in spite of the results shown therein.

8. For these reasons, the board considers that the subject-matter of all claims at issue involves an inventive step.

Adaptation of the description

9. There are no objections to the amendments to the description which have been effected to bring it into line with the claims.

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 maintain the patent on the basis of claims 1 to 17 filed as main request on 29 October 2001 and amended description as requested.

The Registrar:

The Chairperson:

P. Cremona

U. Kinkeldey