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**Datasheet for the decision
of 17 January 2014**

Case Number: T 1457/09 - 3.3.04

Application Number: 99952682.5

Publication Number: 1127068

IPC: C07K 14/47, C07K 4/12,
C07K 7/06, A61K 38/087

Language of the proceedings: EN

Title of invention:
Immunotherapeutic methods using epitopes of WT-1 and GATA-1

Patent Proprietor:
Ganymed Pharmaceuticals AG

Opponent:
Dainippon Sumitomo Pharma Co., Ltd.

Headword:
CTL epitopes of WT-1/GANYMED PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 54(3), 56, 83, 84, 123(2), 123(3)
RPBA Art. 13(3)

Keyword:
"Main request - after amendment: requirements of the EPC met
(yes)"

Decisions cited:
G 0002/98, G 0001/03, G 0002/10, T 0201/83, T 0609/02, T
1396/06, T 1437/07, T 0107/09

Catchword:
See points 34 to 46



Case Number: T 1457/09 - 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 17 January 2014

Appellant I:
(Patent Proprietor)

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Decision under appeal:

**Interlocutory decision of the Opposition
Division of the European Patent Office posted
on 24 April 2009 concerning maintenance of the
European Patent No. 1127068 in amended form.**

Composition of the Board:

Chairman: C. Rennnie-Smith
Members: R. Morawetz
G. Alt

Summary of Facts and Submissions

- I. The appeals by the proprietor (hereinafter "appellant I") and the opponent (hereinafter "appellant II") lie against the interlocutory decision of the opposition division whereby European patent No. EP 1 127 068 was maintained in amended form.
- II. The patent at issue has the title "*Immunotherapeutic methods using epitopes of WT-1 and GATA-1*". It was granted on European patent application No. 99952682.5 which originated from International patent application No. PCT/GB1999/003572 published as WO 00/026249 (hereinafter "application as filed").

Claim 1 as granted read:

"1. A peptide having a molecular weight of 5 000 or less comprising the amino acid sequence RMFPNAPYL or comprising an amino acid sequence, wherein one or both of the amino acids at positions 2 and 9 of the sequence RMFPNAPYL are replaced with another naturally occurring amino acid, wherein said replacement does not abolish binding to HLA-A0201."

- III. Documents cited in this decision:

(D1) EP 1 103 564 A1

(D1a) JP 21809398, priority document of document (D1)

(D2) WO 00/18795

- (D2a) US 09/164,223, first priority document of document (D2)
- (D4) Yasukawa M., Jpn. J. Clin. Hematol. (14 October 1998), vol. 30, page 880, abstract SY-2-5
- (D5) Rammensee H.-G. et al., Immunogenetics (1995), vol. 41, pages 178-228
- (D12) Gagliardi M.C. et al., International Immunology (1995), vol. 7, pages 1741-1752
- (D15) Cole D.J. et al., Cancer Research (1994), vol. 54, pages 5265-5268
- (D17) Kienzle N. et al., Journal of Virology (August 1998), vol. 72, pages 6614-6620
- (D19) Stryer L., Biochemie (1990), Spektrum der Wissenschaft Verlagsgesellschaft mbH, page 22

IV. The patent was opposed under Article 100(a) EPC 1973 on the grounds of lack of novelty (Article 54(3)(4) EPC 1973) and lack of inventive step (Article 56 EPC 1973), under Article 100(b) EPC 1973 and under Article 100(c) EPC 1973 on the ground of added subject-matter (Article 123(2) EPC 1973).

V. The opposition division maintained the patent in amended form on the basis of auxiliary request 3. Claim 1 of auxiliary request 3 read (amendments compared to claim 1 as granted indicated in bold or by strike through):

"1. A peptide **consisting of 9 to 12 amino acids** ~~having a molecular weight of 5 000 or less~~ comprising the amino acid sequence RMFPNAPYL or comprising an amino acid sequence, wherein one or both of the amino acids at positions 2 and 9 of the sequence RMFPNAPYL are replaced with another naturally occurring amino acid, wherein said replacement does not abolish binding to HLA-A0201, **provided that the peptide is not a peptide consisting of the amino acid sequence RMFPNAPYL.**"

- VI. With its statement of grounds of appeal appellant I filed a main request and auxiliary requests 1 to 3, of which auxiliary request 3 corresponded to the claims which were considered by the opposition division to meet the requirements of the EPC.
- VII. With its statement of grounds of appeal appellant II submitted arguments why the claims maintained by the opposition division failed to meet the requirements of the EPC.
- VIII. With a letter of 19 January 2010 appellant I submitted document (D19) and further arguments in response to the statement of grounds of appeal of appellant II.
- IX. With a letter of 21 January 2010 appellant II submitted, in response to the statement of grounds of appeal of appellant I, arguments against all requests on file.
- X. By a communication of 26 July 2013 the parties were summoned to oral proceedings to be held on 16 January 2014.

XI. Oral proceedings took place on 16 January 2014. In the course of the oral proceedings appellant I filed a new main request and withdrew all other pending requests. Independent claims 1, 3, 4, 5, 11, 14, 16 and 17 of the new main request read:

"1. A peptide having a molecular weight of 5 000 or less comprising the amino acid sequence RMFPNAPYL, wherein the peptide includes non-peptide bonds.

3. Use of a peptide having a molecular weight of 5 000 or less comprising the amino acid sequence RMFPNAPYL, provided that the peptide is not (i) a peptide consisting of the amino acid sequence RMFPNAPYL or (ii) a peptide consisting of the amino acid sequence PSQASSGQARMFPNAPYLPSCLE, a polynucleotide encoding said peptide, an expression vector encoding said peptide, or the peptide according to claim 1 or 2 in the manufacture of a medicament for treating cancer in a patient wherein the cancer cells aberrantly express a polypeptide comprising the amino acid sequence RMFPNAPYL.

4. Use of a peptide consisting of the amino acid sequence RMFPNAPYL, a polynucleotide encoding said peptide, or an expression vector encoding said peptide in the manufacture of a medicament for treating cancer in a patient wherein the cancer cells aberrantly express a polypeptide comprising the amino acid sequence RMFPNAPYL.

5. A method for producing activated cytotoxic T lymphocytes (CTL) *in vitro*, the method comprising contacting *in vitro* CTL with antigen-loaded human

class I MHC molecules expressed on the surface of a suitable antigen-presenting cell for a period of time sufficient to activate, in an antigen specific manner, said CTL wherein the antigen is a peptide comprising the amino acid sequence RMFPNAPYL provided that the peptide is not intact human WT-1 polypeptide and further provided that the method is not a method wherein T2 cells (5×10^4) that were irradiated after incubating for 1 hour with the peptide RMFPNAPYL (40 $\mu\text{g/ml}$) and the peripheral blood mononuclear cells (1×10^6) from a healthy human having HLA-A*0201 are co-cultured, one week later, T2 cells that were irradiated after incubating for 1 hour with the peptide (20 $\mu\text{g/ml}$) are added to said culture system for restimulation, from the following day, human IL-2 (final concentration 100 JRU/ml) is added to the culture, and stimulation with the T2 cells that were irradiated after being pulsed with the peptide is repeated for five times.

11. A T cell receptor (TCR) which recognises a cell which aberrantly expresses a polypeptide comprising the amino acid sequence RMFPNAPYL, the TCR being obtainable from an activated cytotoxic T lymphocyte (CTL) obtainable by the method according to any one of Claims 5 to 10 which selectively recognises a cell which aberrantly expresses a polypeptide comprising the amino acid sequence RMFPNAPYL, wherein said activated CTL recognises said cell by binding to the amino acid sequence RMFPNAPYL and wherein said TCR recognises said cell by binding to the amino acid sequence RMFPNAPYL.

14. Use of an activated cytotoxic T lymphocyte (CTL) obtainable by the method according to any one of Claims 5 to 10 which selectively recognises a cell which

aberrantly expresses a polypeptide comprising the amino acid sequence RMFPNAPYL wherein said activated CTL recognises said cell by binding to the amino acid sequence RMFPNAPYL in the manufacture of a medicament for treating cancer in a patient, wherein the cancer cells aberrantly express a polypeptide comprising the amino acid sequence RMFPNAPYL.

16. Use of dendritic cells from a patient in the manufacture of a medicament for treating cancer in said patient wherein the cancer cells aberrantly express a polypeptide comprising the amino acid sequence RMFPNAPYL, wherein said dendritic cells have been contacted in vitro with a peptide having a molecular weight of 5 000 or less comprising the amino acid sequence RMFPNAPYL, provided that the peptide is not (i) a peptide consisting of the amino acid sequence RMFPNAPYL or (ii) a peptide consisting of the amino acid sequence PSQASSGQARMFPNAPYLPSCLE, a polynucleotide encoding said peptide, an expression vector encoding said peptide, or the peptide according to Claim 1 or 2.

17. Use of dendritic cells from a patient in the manufacture of a medicament for treating cancer in said patient wherein the cancer cells aberrantly express a polypeptide comprising the amino acid sequence RMFPNAPYL, wherein said dendritic cells have been contacted in vitro with a peptide consisting of the amino acid sequence RMFPNAPYL, a polynucleotide encoding said peptide, or an expression vector encoding said peptide."

At the end of the oral proceedings the chairman declared the debate closed.

XII. By a communication of 24 January 2014 the parties were informed of the decision of the board.

XIII. The arguments of appellant I, insofar as they are relevant for the main request, can be summarised as follows:

Main request

Admissibility

In this request those claims held by the board to lack novelty had been deleted.

Amendments - Article 100(c) EPC - claim 1

In accordance with decision T 201/83, the application as filed provided a basis for the feature "a *molecular weight of 5000 or less*" on page 7, second paragraph in combination with the specifically disclosed peptides, such as RMFPNAPYL. In this decision the board came to the conclusion that an amendment of a concentration range in a claim was allowable on the basis of a particular value described in a specific example. However, it was not stated that the range needed to have an upper and lower limit. The peptides disclosed in the application as originally filed were characterized by a certain minimum sequence, in particular the sequence RMFPNAPYL, and thus the ranges disclosed in the 2nd paragraph on page 7, i.e. less than 100 000 in molecular weight, preferably less than 50 000, more preferably less than 10 000, could not be read in isolation but

were characterized by a lower limit corresponding to the molecular weight of said minimum sequence.

Amendments - Article 123(2) EPC - claim 3 - disclaimer

The amino acid residue at the left hand side of a peptide sequence is designated by convention, see document (D19), the amino-terminal residue while the amino acid residue at the right hand side of a peptide sequence is designated the carboxy-terminal residue. The term "peptide" was understood to relate to amino acids linked by peptide bonds, hence the term "peptide" in the context of claim 3 related to a peptide consisting of the depicted amino acids linked by peptide bonds. For the skilled person it was thus clear that in claim 3 the regular peptide but not the retro-inverso peptide was disclaimed.

The peptide consisting of the amino acid sequence RMFPNAPYL was disclosed in documents (D1) and (D2), while the peptide consisting of the amino acid sequence PSQASSGQARMFPNAPYLPSCLE was disclosed in document (D2). In the context of the disclaimer, it was not a question of replacing an originally disclosed term "having" by "consisting", but a question of excluding the prior art.

Clarity - Article 84 EPC - claim 5 - disclaimer

The wording of the disclaimer introduced in claim 5 was based on the disclosure of document (D1). The skilled person knew what restimulation of CTLs meant. The average molecular biologist was also familiar with the term "T2 cells". The Enlarged Board had not said in point 3 of the reasons of decision G 1/03 that complex

disclaimers were unallowable, it had said that a disclaimer was not allowable if the necessary limitation could be expressed in simpler terms in positive, originally disclosed features.

Sufficiency of disclosure - Article 83 EPC - claim 3

The argument advanced by appellant II was new and should not be admitted in the proceedings as the subject-matter of claim 3 had been in the proceedings before. The argument was moreover not valid because it was clear to the skilled person that peptides comprising the sequence RMFPNAPYL were cleaved *in vivo* resulting in the presentation of the peptide RMFPNAPYL on the surface of the cell.

Novelty - Article 54(3) EPC - claims 1, 2, 4, 5, 11, 14, 16, 17

Claims 1 and 2 were novel because document (D2) disclosed a peptidomimetic but not a peptide including non-peptide bonds. If -NH₂ and -COOH groups were present, a nonpeptide mimetic could also be coupled via peptide bonds.

Claims 4 and 14 were drafted as referring to a further medical use. Thus, for the assessment whether or not the disclosure of documents (D1) and (D2) was novelty destroying for the subject-matter of these claims it had not only to be examined whether their priority documents (D1a) and (D2a) disclosed the claimed product for the claimed therapeutic application, but also whether these documents provided information other than mere

allegations and verbal statements to the effect that the claimed product was suitable for the claimed therapeutic application.

Document (D1a) did not contain any evidence that CTLs specific for the peptide RMFPNAPYL were able to lyse cancer cells endogenously expressing WT-1 protein. Document (D1a) also did not contain any evidence that cancer cells endogenously expressing WT-1 protein produced the peptide RMFPNAPYL and presented said peptide on their surface in the context of MHC class I antigens. Processing of the WT-1 peptide and transport to the cell surface had not been shown in document (D1a). The pulse experiments did not reflect a therapeutic use in cancer and were not predictive for *in vivo* situations at all. The binding of a WT-1 peptide to MHC molecules and/or the lysis of target cells pulsed with a WT-1 peptide by peptide specific killer T cells was in no way sufficient to indicate a successful killing of tumor cells endogenously expressing WT-1 protein. Information relating to the lysis of tumor cells endogenously expressing WT-1 protein by CTLs was only contained in document (D1), see example 6, but not in document (D1a).

Document (D2a) did not contain any evidence that the peptide RMFPNAPYL or CTLs specific for said peptide were useful in the immunotherapy of cancer. According to page 102 of document (D2) peptide p117-139 comprised two potential MHC binding epitopes. Document (D2) stated on page 102 that peptide p130-138 appeared to be the naturally processed epitope.

Claim 14 was not anticipated by the prior art because neither document (D1a) nor document (D2a) disclosed the processing of WT-1 to the peptide RMFPNAPYL.

The method of claim 5 required the expression of antigen-loaded human class I MHC molecules on the surface of an APC. This feature was not disclosed in document (D2). Document (D2) did not refer to human MHC molecules or APCs. Even if "human" was disclosed in document (D2), it was not disclosed in the context of the method which was cited against claim 5.

Claim 11 related to a T cell receptor (TCR) not to a T cell. It was further required that the TCR recognised said cell by binding to the amino acid sequence RMFPNAPYL. This feature was not disclosed in either document (D1) or (D2). Nowhere was it demonstrated in these documents that WT-1 was processed in the cell and RMFPNAPYL was presented on the surface of the cell.

Claims 16 and 17 were novel because neither document (D1a) nor document (D2a) was enabled for the therapeutic use.

Inventive step - Article 56 EPC

It was conceded that document (D4) was available to the public prior to the priority date of the present patent and represented the closest prior art. The technical problem to be solved was to provide a concrete WT-1 peptide which was useful in cancer therapy. The inventors found that RMFPNAPYL was the naturally processed epitope. Document (D4) did not contain any indication that the peptide RMFPNAPYL was presented by

tumor cells expressing WT-1 rendering it impossible to conclude that CTL specific for said peptide were capable of killing tumor cells expressing WT-1 endogenously and thus, were useful in the treatment of cancer. The proposed solution was not rendered obvious by the prior art because the remaining documents cited by appellant II did not add the elements missing in document (D4) to suggest the subject-matter of the present patent. It was not denied that the screening could be done but the question to be addressed was whether the prior art provided the skilled person with any hints to the claimed subject-matter. It was not known whether there was a HLA-A*0201 binding epitope at all. Document (D4) provided no hint to search in the Caucasian population. Pure binding motifs provided at best a hint and could be misleading as acknowledged in document (D5) on page 183, in the first paragraph in the left hand column. Further testing and further results were necessary to identify a peptide as being useful. It had not been straightforward to identify RMFPNAPYL as the relevant peptide, as could be seen from page 102 of document (D2). Here the peptide was identified as not being useful.

XIV. The arguments of appellant II, insofar as they are relevant for the main request, can be summarised as follows:

Main request

Admissibility

This request was late filed and therefore inadmissible.

Amendments - Articles 100(c) and 123(2) EPC

Decision T 201/83 related to situations where intervals confined by defined lower and upper limits had been further limited by amendment. The present case was not analogous. There was no defined lower limit in the application as filed. The sequence RMFPNAPYL could not implicitly define a lower limit because precisely this sequence was disclaimed.

The disclaimer in claim 3 removed more from the claims than had been disclosed in the prior art because the term "peptide" embraced peptides with normal peptide bonds and retro-inverso peptides, see paragraph [0011] of the patent. The patent was silent about any specific designation scheme that would distinguish retro-inverso from normal peptides other than the explicit recitation of the qualifier "retro-inverso". Any indication being absent from the claims that either only a retro-inverso peptide or only a peptide connected by normal CO-NH peptide bonds would be intended, the term had to be understood as embracing both forms. Neither document (D1) nor (D2) described retro-inverso peptides. Therefore claim 1 was in breach of the requirements expressed in decision G 1/03 of the Enlarged Board of Appeal.

The replacement of "having" with "consisting of" in the disclaimer of claim 3 was not supported by the application as filed and violated Article 123(2) EPC.

Clarity - claim 5

The reading of claim 5 was difficult and the disclaimer contained in the claim was not concise, contrary to the requirements laid down in point 3 of the reasons of decision G 1/03. It was not clear whether or not the restimulation was part of the "five times". The term "T2 cells" was an internal designation and thus unclear.

Sufficiency of disclosure - claim 3

The subject-matter of claim 3 was not sufficiently disclosed because it extended to the use of variants and the only peptide shown in the patent to have any effect was the peptide RMFPNAPYL, which was disclaimed. This was not a new argument, as it had been set out in the grounds of appeal under the heading of Article 56 EPC.

Novelty - Article 54(3) EPC - claims 1, 2, 4, 5, 11, 14, 16, 17

Claims 1 and 2 were anticipated by the disclosure of mimetics of WT-1 on page 18, lines 15 to 25 of document (D2) corresponding to the disclosure in the paragraph bridging pages 15 and 16 of document (D2a). A non-peptide mimetic formed from building blocks which were not amino acids inevitably contained non-peptide bonds.

Applying the standards of decision T 609/02 claim 4 was anticipated by document (D1) because document (D1a), the priority document of document (D1), provided an enabling disclosure of the medical use. Document (D1a) provided textual support, explanation and confirmation of the use of WT-1-derived peptides as cancer vaccines. Examples 1

to 3 were present in both documents (D1a) and (D1). The killing of cells pulsed with the peptide having the sequence RMFPNAPYL as shown in the examples 1 to 3 of document (D1a) was evidence of a direct and specific effect. See also the conclusion at the end of page 17 of document (D1a). Also document (D2) anticipated claim 4, see page 4 to 7 and page 35, lines 7 ff.

The subject-matter of claim 5 was anticipated by document (D2), pages 27 and 28 in combination with page 14, line 25, see section 4.3 of the written submission of 1 October 2008. "Human" was mentioned in connection with a pharmaceutical composition in document (D2) on page 31 and in document (D2a) on page 28.

Claim 14 was anticipated by documents (D1) and (D2). The method disclosed in document (D1) and disclaimed in claim 5 delivered a pharmaceutical composition comprising CTLs. Claim 28 of document (D2) related to a pharmaceutical composition comprising a T-cell that specifically reacted with a WT-1 polypeptide.

Claims 16 and 17 differed from previous claim 27 only in that the sequence of the peptide was defined differently. Dendritic cells were mentioned in document (D2) on page 12, line 19 and in document (D2a) on page 9, line 28. It was evident that treatment of malignant disease was envisaged, see the respective preceding sentence in both documents. Since according to page 27, lines 21 to 23 of document (D2) "*T-cells may be stimulated with [...] an antigen-presenting cell (APC) that expresses a WT1 polypeptide*", and furthermore noting that this disclosure was in the context of "*immunotherapeutic compositions*" (page 27, line 12) it

followed that the medical use of dendritic cells in the treatment of cancer was clearly envisaged in document (D2).

Inventive step

On the front page of document (D4) the indication "Receiving stamp by National diet library, October 14, 1998" was present. Document (D4) was thus available to the public at the relevant date. Document (D4) might be considered to represent the closest prior art. While document (D4) related to the most common haplotypes among the Japanese population, the contested patent related to the haplotype which was most common in the Caucasian population (HLA-A*0201). The problem to be solved could be defined as the provision of a similar treatment for a different population. The skilled person would consider document (D5) and would apply its teaching. Starting from document (D4) which identified WT-1 as a tumor antigen and provided the incentive combined with the information provided in document (D5), the skilled person would investigate the WT-1 sequence and identify possible HLA-A*0201 binding peptides in a straightforward manner. Only diligence but not inventive activity was required to filter out those sequences that bound to HLA-A*0201 and were effective in a killing assay. Cancer and in particular leukemia were not rare diseases and the skilled person confronted with document (D4) would of course extend the teaching to other populations. Document (D4) established WT-1 as a therapeutic target. The peptide was obvious in view of the prior art because only routine tests were required to identify it, reasonable expectation of success was thus given. Document (D2) had used the bimas algorithm

and had identified the RMFPNAPYL sequence as having the highest score for HLA-A*0201 binding, see Table 3. It was not denied that a validation of the identified peptides was required, but this validation of the peptide was routine.

- XV. Appellant I requests that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed during the oral proceedings. Appellant II requests that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

Main request

Admissibility

1. The main request was filed during the oral proceedings after the board had expressed its view that the subject-matter of the then pending claim request lacked novelty vis-à-vis document (D2). Appellant II considered the request as late-filed and therefore inadmissible.
2. This request differs from the then pending request in the deletion of claims the subject-matter of which was considered as not novel and consequential amendments such as cross-references and claim dependencies. These amendments were made in response to an objection raised for the first time during the oral proceedings by the board. Accordingly, they could not have been filed earlier. These amendments are straightforward, they do not raise new issues, do not contribute to the

complexity of the appeal case and did not require a postponement of the oral proceedings. The board, exercising its discretion under Article 13(3) RPBA, admits the request in the proceedings.

Amendments - Article 100(c) EPC - claim 1

3. In the decision under appeal, the opposition division held (see reasons, point 1.1) that the feature "*having a molecular weight of 5 000 or less*" had no basis in the application as filed. Appellant I contested this decision.

4. According to Article 123(2) EPC the European patent application or European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. Amendments are permitted within the limits of what the skilled person would derive, directly and unambiguously and using common general knowledge, from the application as filed (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, section II.E.1).

5. According to page 7, lines 10 to 13 of the application as filed "*The peptides of the invention may be of any size, but typically they may be less than 100 000 in molecular weight, preferably less than 50 000, more preferably less than 10 000 and typically about 5 000.*" On page 9, lines 9 to 14 the application as filed discloses that: "*It is well known that an optimum length for a peptide to bind to an HLA molecule is around 8 to 12 amino acids, preferably 9 amino acids. Particularly preferred peptides of the invention are those consisting*

of the amino acid sequences RMFPNAPYL or CMTWNQMNL or HLMPFPGPLL."

6. In the board's judgement, in the light of the application as a whole, in particular considering the size of the peptides disclosed on page 9, the skilled person would have understood that the feature "less than" in the context of "less than 100 000", "less than 50 000" and "less than 10 000" in the passage on page 7 means that the indicated ranges encompass peptides with a molecular weight of less than 5 000, considering that a molecular weight of 5 000 corresponds approximately to a peptide with 45 amino acid residues, while the optimum length disclosed in the application as filed is around 8 to 12 and the length of the preferred peptides is 9 or 10 amino acids. Moreover, the passage on page 7 clearly identifies the value "5 000" as a point within a range of possibilities which may therefore mark an end-point for a particular sub-range in accordance with decision T 201/83 (OJ EPO 1984, 481, reasons, points 8 and 9). Therefore the feature "5 000 or less" is directly and unambiguously derivable from the application and the amendment is allowable under Article 123(2) EPC.

7. Appellant II submitted that the rationale of decision T 201/83, *supra*, was only applicable for cases wherein a range was defined by a defined lower and a defined upper limit. The board is not persuaded. Although in the case underlying decision T 201/83, *supra*, the end points of the range were indeed defined, this played no role in the considerations of the board. It is stated in decision T 201/83 (*supra*, reasons, point 8) that: "*The question then arises whether or not the skilled reader could have envisaged the new range within the old one by*

extracting one specific value from the context of the disclosure." Thus, decision T 201/83, *supra*, does not state that the range necessarily needs to have a defined lower and upper limit and in the view of the board no such requirement can be derived from what has been explicitly stated in decision T 201/83, *supra*, either.

8. Appellant II further submitted that the sequence RMFPNAPYL could not implicitly define a lower limit because precisely this sequence was disclaimed. In the board's judgement this argument fails for several reasons. Firstly, although the use of the peptide RMFPNAPYL is disclaimed in claims 3 and 16 of the main request, the peptide itself is not disclaimed in any of the claims of the main request. Secondly, it is the content of the application as filed which is decisive for the determination of the compliance of an amendment with the requirements of Article 123(2) EPC. The peptide RMFPNAPYL is undeniably disclosed in the present application as filed. Finally, the disclaimed sequence is not used as a lower limit anyway and the application as filed discloses peptides other than the peptide RMFPNAPYL, with a molecular weight of less than 5 000.

Amendments - Article 123(2) EPC - claim 3 - disclaimer

9. During the proceedings before the department of first instance appellant I introduced a disclaimer which aimed at excluding the novelty-destroying disclosure of intermediate prior art documents (D1) and (D2). In the main request submitted by appellant I with its letter of 23 March 2007 the disclaimer read "*provided that the peptide is not (i) a peptide having the amino acid*

sequence RMFPNAPYL or (ii) a peptide having the amino acid sequence PSQASSGQARMFPNAPYLPSCLE". (Emphasis added).

10. In claim 3 of the present main request the disclaimer is worded as follows "*provided that the peptide is not (i) a peptide consisting of the amino acid sequence RMFPNAPYL or (ii) a peptide consisting of the amino acid sequence PSQASSGQARMFPNAPYLPSCLE". (Emphasis added).* Appellant II held (i) that the disclaimer removed more than was necessary to restore novelty vis-à-vis documents (D1) and (D2) and (ii) that replacement of the term "*having*" initially used in the disclaimer by the term "*consisting of*" presently used was not supported by the application as filed and violated Article 123(2) EPC.
11. As to the first objection, the board notes that pursuant to decision G 1/03 (OJ EPO 2004, 413, reasons, point 3) a disclaimer should not remove more than is necessary to restore novelty. It is common ground that documents (D1)/(D1a) disclose (see paragraph [0022]/paragraph [0017]) the peptide with the sequence RMFPNAPYL, denoted as D^b 126, while documents (D2)/(D2a) disclose (see Tables III and XLV in both documents) the peptides RMFPNAPYL and PSQASSGQARMFPNAPYLPSCLE.
12. Appellant II submitted that according to paragraph [0011] of the patent in suit the term "peptide" also included retro-inverso peptidomimetics. Therefore the disclaimer in claim 1 excluded also retro-inverso peptides of the respective sequences which were not disclosed in documents (D1) and (D2).
13. The meaning of terms in a claim has to be determined from the point of view of the skilled person, who reads

the claim in the context of the patent and against the background of his/her common general knowledge. The board notes that the "peptides" are defined in the disclaimer as "*consisting of the amino acid sequence RMFPNAPYL*" or as "*consisting of the amino acid sequence PSQASSGQARMFPNAPYLPSCLE*". The skilled person knows that peptides consist of L amino acids joined by peptide bonds (CO-NH). According to conventional nomenclature in the field of peptides (see e.g. page 22 of document (D19)) the amino acid residue at the left hand side of a peptide sequence - R in the case of RMFPNAPYL - designates the amino-terminal residue while the amino acid residue at the right hand side of a peptide sequence - L in the case of RMFPNAPYL - designates the carboxy-terminal residue. In contrast, in a retro-inverso peptide the L amino acids are replaced by D amino acids (inverso) and the order is reversed (retro). As a result the peptide bonds are reversed, i.e. the amino acid residues are joined by (-NH-CO-) bonds. Retro-inverso RMFPNAPYL would be depicted as HO₂C-RMFPNAPYL-NH₂.

14. From the depiction of the sequences in claim 3 it is thus evident for the skilled person that the term "peptide" does not extend to retro-inverso peptides in the context of claim 3 and that therefore the disclaimed peptides are the regular peptides in which the amino acids are joined by peptide (-CO-NH-) bonds. Accordingly, in the board's judgement, the disclaimer removes the peptides RMFPNAPYL and PSQASSGQARMFPNAPYLPSCLE, but not their retro-inverso isomers and therefore does not remove more than is necessary to restore novelty.

15. As to the second objection, the board notes that pursuant to decision G 1/03 (supra, reasons, points 2.1.3 and 3) "*Such a disclaimer, only excluding subject-matter for legal reasons, is required to give effect to Article 54(3) EPC and has no bearing on the technical information in the application. It is, therefore, not in contradiction to Article 123(2) EPC*" and "*(...) an allowable disclaimer merely restricts the required protection and is outside the scope of Article 123(2) EPC, which does not allow the subject-matter of an application to be extended beyond the content of the application as filed.*" Therefore, in the present circumstances the question of whether or not terms used in the disclaimer are supported by the description does not arise and the change of the term "*having*" to the term "*consisting of*" cannot possibly offend against Article 123(2) EPC. The board is also satisfied that the term "*consisting of*" adequately reflects the disclosure of the conflicting prior art documents (D1) and (D2) and that the disclaimer is thus properly drafted. Appellant II did not raise an objection that the subject-matter remaining in the claim after introduction of the disclaimer contravenes the requirements of Article 123(2) EPC. Also the board has no objection (see decision G 2/10, OJ 2012, 376, Headnotes 1a and 1b).
16. For the reasons indicated above the board decides that the main request complies with the requirements of Article 100(c) EPC and Article 123(2) EPC.

Article 123(3) EPC

17. Appellant II did not raise any objections under Article 123(3) EPC. The main request differs from the

claims as granted in the restriction or deletion of several claims and the introduction of disclaimers in claims 3, 5 and 16 (see section XI above). These amendments restrict the scope of protection conferred by the claims vis-à-vis the protection conferred by the claims of the granted patent and the board is thus satisfied that the requirements of Article 123(3) EPC are fulfilled.

Clarity - Article 84 EPC - claim 5 - disclaimer

18. Appellant II submitted that the disclaimer introduced in claim 5 was neither concise nor clear, contrary to the requirements set out in decision G 1/03, *supra*, Headnote 2.4.

19. The disclaimer present in claim 5 excludes the novelty-destroying disclosure of example 3 in document (D1). The wording of the disclaimer follows closely the disclosure of document (D1), see page 6, lines 26 to 34 and recites the necessary steps for the induction of CTLs as disclosed in this example. The board considers that in the present case the necessary limitation cannot be expressed in simpler terms in positive, originally disclosed features. The board also considers that the terminology used is clear to the person skilled in the field. The skilled person is in particular familiar with the term "T2 cells" as these cells were commonly used in the field before the priority date of the patent in suit, see e.g. document (D12) on page 1742, left hand column, third paragraph; document (D15) on page 5265, right hand column, fifth paragraph and document (D17) on page 6615, left hand column, first full paragraph. The skilled person, familiar with the induction of CTLs *in vitro*,

would also have no difficulty in understanding that after initial co-culture of peripheral blood mononuclear cells (PBMCs) with T2 cells and a first restimulation with pulsed, irradiated T2 cells, this stimulation is repeated five times with pulsed, irradiated T2 cells.

20. The board concludes that claim 5 meets the requirements of Article 84 EPC.

Sufficiency of disclosure - claim 3

21. At the oral proceedings before the board appellant II raised a fresh objection under Article 83 EPC against claim 3 submitting that the subject-matter of the claim was insufficiently disclosed because the only peptide shown to have any effect in the patent in suit was disclaimed. Appellant I objected to the admissibility of the objection at this late stage of the proceedings and requested that it be dismissed.
22. The board sees no need to decide on the admissibility of the objection as it considers that it is without any merit anyway, see below point 24.
23. It is undisputed by appellant II that the patent in suit provides evidence that CTLs specific for the peptide RMFPNAPYL kill tumour cells expressing WT-1 and HLA-A*0201 (see paragraphs [0122] to [0132]). The specific peptide sequence RMFPNAPYL is disclaimed in claim 3. However, in the board's judgement this has no bearing on the sufficiency of disclosure of the subject-matter of claim 3.

24. The person skilled in the field of immunology is generally aware that antigen-processing cells (APCs) process proteins intracellularly, this is also mentioned in the patent in suit (see paragraph [0024]). This processing results in the peptides which are ultimately expressed in the context of MHC class I antigens on the surface of APCs. The patent provides experimental evidence that RMFPNAPYL is a natural CTL epitope (see paragraphs [0122] to [0132]). The peptide binds HLA-A*0201, and the HLA-A*0201-RMFPNAPYL complex, when present on the surface of a suitable APC is capable of eliciting the production of CTLs which recognise cells aberrantly expressing a polypeptide comprising the amino acid sequence RMFPNAPYL, such as WT-1 expressing tumor cells. The board is thus satisfied that the skilled person would, on the basis of the guidance provided in the patent in suit (see paragraphs [0122] to [0132]) together with his or her common general knowledge at the priority date of the patent, have readily understood that peptides comprising the amino acid sequence RMFPNAPYL are processed by APCs to the peptide consisting of the sequence RMFPNAPYL and thus that the claimed peptides, which are defined as *"a peptide having a molecular weight of 5 000 or less comprising the amino acid sequence RMFPNAPYL, provided that the peptide is not (i) a peptide consisting of the amino acid sequence RMFPNAPYL or (ii) a peptide consisting of the amino acid sequence PSQASSGQARMFPNAPYLPSCLE"* are suitable for the claimed therapeutic application.
25. For these reasons appellant II's objection is dismissed.

Novelty - Article 54(3) EPC - claims 1 and 2

26. Documents (D1) and (D2) are the only documents cited in the appeal proceedings under Article 54 EPC, more particularly under Article 54(3) EPC. It is common ground that only the disclosure of document (D1), as far as it is entitled to the claimed priority of document (D1a), and only the disclosure of document (D2), as far as it is entitled to the first priority claimed of document (D2a), can be considered relevant prior art under Article 54(3) EPC for the claimed subject-matter.
27. In the decision under appeal (see reasons, section 2.3) the opposition division held that the subject-matter of claims 3 and 4 of auxiliary request 1 before it was novel. Appellant II appealed this decision and submitted that page 18, lines 15 to 25 of document (D2) anticipated the subject-matter of present claims 1 and 2. It is common ground that the relevant disclosure is present in document (D2a), on page 15, line 23 to page 16, line 3.
28. According to established case law, claimed subject-matter lacks novelty if it is directly and unambiguously derivable from the prior art (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, section I.C.3.1).
29. Claims 1 and 2 relate to peptides including non-peptide bonds while document (D2) discloses mimetics of WT-1 polypeptides. These mimetics may (i) either comprise amino acids linked to one or more amino acid mimetics or (ii) may be entirely non-peptide mimetics, i.e.

- compounds that do not contain amino acids (see page 18, lines 15 to 25).
30. As regards the first type of mimetics the board notes that document (D2) is silent as regards the nature of the bonds between the above mentioned components in the mimetics. Appellant II argued that the possibility of forming peptide bonds when joining amino acids and amino acid mimetics did not exist, accordingly the bonds necessarily had to be non-peptide bonds in these types of mimetics disclosed in document (D2).
31. The board is not persuaded. There is no sound reason why the amino acid mimetics of document (D2) should not comprise carboxyl- and aminogroups especially if, as is the case in document (D2), they are used in mimetics wherein amino acids, which per definition comprise carboxyl- and aminogroups, are linked to one or more of the amino acid mimetics. The skilled person knows that when the carboxyl group of one molecule reacts with the amino group of another molecule, peptide bonds (CO-NH) are formed between two molecules. In the board's judgement it is thus by no means evident that the bonds in the mimetics of document (D2) are inevitably non-peptide bonds.
32. As regards the second type of mimetics the board considers that mimetics that are entirely non-peptide mimetics and do not contain a single amino acid do not qualify as peptides.
33. Therefore the subject-matter of claims 1 and 2 is not directly and unambiguously derivable from document (D2).

Novelty - Article 54(3) EPC - claim 4

34. Claim 4 is drafted as a second medical use claim (see section XI above for the complete wording of the claim).

Document (D1)

35. In the decision under appeal (see reasons, section 2.3) the opposition division held that the subject-matter of claim 14 of auxiliary request 1 before it, which corresponds to the subject-matter of present claim 4, was anticipated by the intermediate document (D1). The opposition division considered that both documents (D1) and (D1a) disclosed pharmaceutical compositions comprising the peptide RMFPNAPYL and their use as a cancer vaccine. Appellant I appealed this decision.

36. Pursuant to established case law, a disclosure destroys novelty only if the teaching it contains is reproducible, in other words if it can be carried out by the person skilled in the art (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, section I.C.3.11, and in particular decision T 1437/07 of 26 October 2009, reasons, points 25 and 26 cited in that section). For the requirement of reproducibility to be considered as fulfilled in relation to a medical use it is necessary - following the principles developed by the case law in the framework of the evaluation of Article 83 EPC in the case of a second medical use claim (see decision T 609/02 of 27 October 2004, reasons point 9) - that the disclosure in the prior art document is such as to make it credible that the therapeutic effect on which the disclosed treatment relies can be achieved. Thus, in the present case a prior art document is novelty-

- destroying only if it discloses not only the product referred to in the claim - here RMFPNAPYL - for the claimed therapeutic application - here treatment of cancer - but also that the claimed product is indeed suitable for the claimed therapeutic application.
37. In the present circumstances (see point 26 above), for document (D1) to anticipate the subject-matter of claim 4, the suitability of RMFPNAPYL for the therapeutic application must be disclosed in both the priority document (D1a) and in document (D1). This follows from Article 89 EPC in combination with decision G 2/98 (OJ EPO 2001, 413, reasons, point 9) wherein the Enlarged Board endorsed a narrow or strict interpretation of the concept of "the same invention", limiting the right to priority to subject-matter which the person skilled in the art can derive directly and unambiguously, using common general knowledge, from the previous application as a whole, see also decision T 107/09 of 12 July 2012 (reasons, points 7 to 10).
38. In the present case, the claimed therapeutic application - treatment of cancer - is based on the finding that tumor reactive CTLs mediate tumor regression in animal models and in man (see e.g. patent in suit, paragraph [0002]). Tumor reactive CTLs recognize processed antigen presented on the tumor cell by MHC class I molecules. They bind to the complex of the MHC class I and the antigen and kill the tumor cell. CTL lysis thus requires that the target peptides are endogenously processed and presented in association with class I MHC molecules on tumor cells. Therefore, to show the suitability of the peptide RMFPNAPYL for the treatment of cancer, in the board's judgement, it is required that it is at least

shown in the prior art that CTLs specific for the peptide RMFPNAPYL are able to lyse cancer cells endogenously expressing WT-1 protein or at least that cancer cells endogenously expressing WT-1 protein produce the peptide RMFPNAPYL and also present said peptide on their surface in the context of MHC class I molecules.

39. Document (D1) relates to tumor antigens based on the products of WT-1 and discloses the peptide D^b 126 with the sequence RMFPNAPYL (see paragraph [0022]), that cytotoxic T cells (CTLs) can be raised against this peptide in C57BL/6 mice injected with the peptide (see example 1), that effector cells derived from the lymph nodes of mice immunized with the D^b 126 peptide killed target cells pulsed with said peptide but did not kill target cells that were not pulsed with said peptide (see example 2), and an *in vitro* method for the induction of CTLs (see example 3). In example 6 it was tested whether the D^b 126 peptide-specific CTLs can recognize tumor cells that inherently express WT-1 and can cause cytolysis thereof. It was found that the D^b 126 peptide-specific CTLs caused lysis of the FBL3 cells that inherently express WT-1 but not the RMA cells that do not express WT-1. Document (D1) concludes at the end of example 6 that "*These results suggest that the D^b 126 peptide-specific CTL can recognize D^b 126 peptide or the related peptides, which were naturally produced by the intracellular processing of the WT1 protein and presented on the H-2D^b molecules of the WT1-expressing cells*". Thus, example 6 is that example of document (D1) that provides the necessary evidence which renders the technical effect (treatment of cancer) plausible in that the results obtained in this experiment suggest that the

- D^b 126 peptide-specific CTLs can recognise D^b 126 peptide or the related peptides, which are naturally produced by the intracellular processing of the WT-1 protein and presented on the H-2D^b molecules on WT-1-expressing cells.
40. Its priority document (D1a) differs from document (D1) in that document (D1a) only comprises examples 1 to 3 of document (D1) and in particular in that document (D1a) does not comprise example 6 of document (D1). Further, document (D1a) does not contain any evidence that CTLs specific for the peptide RMFPNAPYL are able to lyse cancer cells endogenously expressing WT-1 protein. Document (D1a) also does not contain any evidence that cancer cells endogenously expressing WT-1 protein produce the peptide RMFPNAPYL and present said peptide on their surface in the context of MHC class I antigens. The experimental results disclosed in document (D1a) are therefore not sufficient to make it credible that the RMFPNAPYL peptide is suitable for the treatment of cancer (cf decision T 609/02, *supra*, reasons, point 9).
41. Appellant II argued that document (D1a) taught the use of WT-1 derived peptides as cancer vaccines and provided an enabling disclosure of the medical use because the killing of cells pulsed with the peptide having the sequence RMFPNAPYL, as shown in the examples 1 to 3 of document (D1a), was evidence of a direct and specific effect. Moreover, document (D1a) stated (see page 17, lines 15 to 18) that the results demonstrated that the D^b 126 peptide functioned indeed as a tumor antigen and that it induced the growth of killer T cells against tumor cells.

42. The board is not persuaded by this argument. Document (D1a) does indeed state on page 17, lines 15 to 21 that "*The above results demonstrated that the peptide of the present invention indeed functions as a tumor antigen and that it induced the growth of killer T cells (tumor cell-toxic T cells) against tumor cells. Therefore, the tumor antigen peptide of the present invention is useful as a cancer vaccine for leukemia and solid tumors that are accompanied by increased expression of the WT1 gene*". However, the observation that cells pulsed with a peptide *in vitro* are killed by cells raised against this very peptide does not allow any conclusion as regards the *in vivo* processing and presentation of the peptide on tumor cells endogenously expressing WT-1 protein. Therefore the above statement is a mere assertion uncorroborated by experimental data. As a matter of fact, the induction of CTLs against tumor cells has not been shown in document (D1a). Consequently, the suitability of the peptide RMFPNAPYL for the treatment of cancer is not disclosed in document (D1a), and document (D1) does not destroy the novelty of the subject-matter of claim 4.

Document (D2)

43. Document (D2) is like document (D1) an intermediate document. Appellant I argued that the priority document (D2a) did not contain any evidence that the peptide RMFPNAPYL or CTLs specific for said peptide were useful in the immunotherapy of cancer.
44. Document (D2) discloses polypeptides comprising an immunogenic portion of native WT-1 including the peptides p126-132 (RMFPNAPYL) and p117-139 (PSQASSGQARMFPNAPYLPSCLE) (see Tables III and XLV), the

identification of an immune response to WT-1 in patients with haematological malignancies (see example 1), the induction of antibodies to WT-1 in mice immunised with cell lines expressing WT-1 (see example 2), the induction of T helper (Th) and antibody responses in mice immunised with WT-1 peptides (see example 3), the induction of CTL responses in mice immunised with WT-1 peptides (see example 4 and Figures 9A and 9B), the use of the WT-1 polypeptide p117-139 to elicit WT-1 specific CTL in mice and also that CTL specific for p117-139 lysed targets incubated with p117-139 peptides and also lysed malignant cells expressing WT-1 (see example 5 and Figure 11B). Document (D2) states on page 101, lines 14 to 15 that "*CTL lysis demands that the target WT1 peptides are endogenously processed and presented in association with tumor cell class I MHC molecules*". The results obtained in example 5 confirm that WT-1 peptide specific CTL specifically kill malignant cells by recognition of processed WT-1, but only p130-138 specific CTL showed lysis of a WT-1 positive tumor cell line. Document (D2) concludes that p130-138 (NAPYLPSC) appears to be the naturally processed epitope.

45. The major difference between document (D2) and its priority document (D2a) is that although example 5 of document (D2a) discloses the use of WT-1 polypeptide p117-139 to elicit WT-1 specific CTLs in mice and that CTLs specific for p117-139 lysed malignant cells expressing WT-1, it does not identify the segment within p117-139 which is the naturally processed epitope presented in association with class I MHC molecules by WT-1 positive tumor cells. In fact, neither document (D2a) - nor document (D2) - does contain any evidence that CTLs specific for the peptide RMFPNAPYL are able to

lyse cancer cells endogenously expressing WT-1 or that cancer cells endogenously expressing WT-1 protein produce the peptide RMFPNAPYL and also present said peptide on their surface in the context of MHC class I molecules. The board concludes that the evidence in document (D2a) is not sufficient to make it credible that any of the compounds referred to in claim 4 are suitable for the treatment of cancer. Therefore document (D2) does not destroy the novelty of the subject-matter of claim 4.

46. To sum up, the subject-matter of claim 4 is not anticipated by either document (D1) or (D2).

Novelty - Article 54(3) EPC - claim 14

47. Claim 14 is also drafted as a further medical use claim and relates to the use of an activated CTL which selectively recognises a cell which aberrantly expresses a polypeptide comprising the amino acid sequence RMFPNAPYL wherein said activated CTL recognises said cell by binding to the amino acid sequence RMFPNAPYL in the manufacture of a medicament for treating cancer in a patient.
48. Similarly as set out above for claim 4 (see points 36 to 38), to conclude that CTLs which bind to the amino acid sequence RMFPNAPYL are suitable for the treatment of cancer, it is required that evidence is provided demonstrating that CTLs specific for the peptide RMFPNAPYL are able to lyse cancer cells endogenously expressing WT-1 protein or at least that cancer cells endogenously expressing WT-1 protein produce the peptide

RMFPNAPYL and also present said peptide on their surface in the context of MHC class I molecules.

49. Neither document (D1a) nor document (D2a) provides the necessary evidence (see points 40 and 45 above). The board concludes that neither document (D1a) nor document (D2a) renders the claimed therapeutic application, i.e. treatment of cancer, plausible. Therefore the subject-matter of claim 14 is not anticipated by either document (D1) or (D2).

Novelty - Article 54(3) EPC - claim 5

50. Claim 5 relates to a method for producing activated CTLs *in vitro* and corresponds to claim 15 of auxiliary request 1 before the opposition division. The opposition division has held that this claim was novel. Appellant II has appealed this decision and submitted that the section under the heading "*T cells*" present in document (D2) on page 27, line 11 to page 30, line 29 together with the disclosure on page 31, lines 15 to 17 of document (D2) disclosed all the features of claim 5. It is common ground that the corresponding disclosure is present in document (D2a), see page 24, line 20 to page 28, line 7 and page 28, lines 23 to 25.
51. Document (D2) discloses the following in the passage referred to by appellant: that T cells may be stimulated with an APC that expresses a WT-1 polypeptide and that such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the WT-1 polypeptide. This passage thus relates to the generation of T cells that are specific for the WT-1 polypeptide, but not to the activation of

already generated CTLs. Pursuant to document (D2) to expand the CD8+ T cells in number, the cells can be re-exposed to WT-1 polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a WT-1 polypeptide (page 29, lines 8 to 14). Page 31, lines 15 to 17 discloses that within certain embodiments, pharmaceutical compositions and vaccines are designed to elicit T cell response specific for a WT-1 polypeptide in a patient, such as a human.

52. The method of claim 5 requires "*contacting in vitro CTL with antigen-loaded human class I MHC molecules expressed on the surface of a suitable APC*" (emphasis added). It follows from point 51 above that a) document (D2) discloses re-exposure to stimulator cells that synthesize a WT-1 polypeptide, that b) the feature "*human*" is disclosed on page 31, but not in the context of the method which is cited against claim 5, and that c) the passage relied on by appellant II is silent as to the nature of the stimulator cells and in particular does not refer to human class I MHC or human APC in this context. Therefore, document (D2) does not disclose all the features of the method of claim 5 in combination.

53. The subject-matter of claim 5 is not directly and unambiguously derivable from document (D2).

Novelty - Article 54(3) EPC - claim 11

54. In the decision under appeal (see section 2.3) the opposition division held that the subject-matter of claim 21 of auxiliary request 1 before it, which

corresponds to that of present claim 11, was anticipated by document (D1). Appellant I appealed this decision.

55. Claim 11 relates to a T cell receptor (TCR) which recognises a cell which aberrantly expresses a polypeptide comprising the amino acid sequence RMFPNAPYL, wherein said TCR recognises said cell by binding to the amino acid sequence RMFPNAPYL.
56. Document (D1a) discloses CTLs raised against cells pulsed with peptide RMFPNAPYL (see example 2) but does not disclose CTLs which selectively recognise a cell which aberrantly expresses a polypeptide comprising the amino acid sequence RMFPNAPYL. Document (D1a) also does not contain any evidence that cells aberrantly expressing WT1 protein produce the peptide RMFPNAPYL and present said peptide on their surface in the context of MHC class I antigens. Accordingly, the feature "*T cell receptor (TCR) which recognises a cell which aberrantly expresses a polypeptide comprising the amino acid sequence RMFPNAPYL, wherein said TCR recognises said cell by binding to the amino acid sequence RMFPNAPYL*" is not disclosed in document (D1a) and therefore document (D1) does not anticipate the subject-matter of claim 11 (see point 26 above).

Novelty - Article 54(3) EPC - claims 16 and 17

57. In the decision under appeal (see reasons, section 2.3) the opposition division held that the subject-matter of claims 26 and 27 of auxiliary request 1 before it, which corresponds to that of present claims 16 and 17, was novel vis-à-vis document (D1). Appellant II appealed this decision and submitted that the medical use of

- dendritic cells (DCs) in the treatment of cancer was clearly envisaged in document (D2).
58. Claims 16 and 17 are drafted as further medical use claims (see section XI above for the complete wording of the claims). As a consequence, a prior art document is novelty-destroying only if it not only discloses the claimed product - here DCs - for the claimed therapeutic application - here treatment of cancer - but also that the claimed product is indeed suitable for the claimed therapeutic application (see point 36 above). Thus, that a "medical use is envisaged" is not the relevant criterion for the present assessment.
59. The passages of document (D2a) relied on by appellant II do not allow any conclusion regarding the suitability of the disclosed DCs to achieve the therapeutic effect. It is generally known that DCs are professional APCs which present intracellularly processed antigen in the context of MHC class I on their surface and stimulate CTL responses against the antigen. This is the rationale underlying the use of DCs in cancer therapy (see also patent in suit, paragraphs [0019], [0070], and [0076]). However, as set out above (see point 45), document (D2a) fails to identify the RMFPNAPYL peptide as the natural CTL epitope. *A fortiori* document (D2a), and in particular the passages relied on by appellant II, do not disclose the claimed therapeutic use which relies on RMFPNAPYL being the natural CTL epitope. Therefore document (D2) does not anticipate the subject-matter of claims 16 and 17.
60. No further objections were raised by appellant II under Article 54(3) EPC and the board is satisfied that the

subject-matter of all claims is novel within the meaning of Article 54(3) EPC over the disclosure of documents (D1) and (D2).

Inventive step

Closest prior art

61. In the oral proceedings before the board the parties agreed that the publication date of document (D4) was 14 October 1998, that the document thus belonged to the state of the art and that it represented the closest prior art. The board sees no reasons to differ and, hence, takes document (D4) as the starting point when assessing inventive step.

62. Document (D4) is an abstract which reports on a study in which the function of CTLs specific for peptides derived from WT-1 on leukemia cells was assessed. Starting from the amino acid sequence of WT-1, 9-mer peptides comprising binding motifs for HLA-A*2402 (one of the most frequent HLA subtypes in the Japanese population) were synthesized. Dendritic cells established by culturing PBMCs of HLA-A*2402-positive healthy individuals in the presence of IL-4, GM-CSF, and TNF- α were pulsed with WT-1 peptides, and used to stimulate CD8+ T cells repeatedly. A CD8+ T cell clone specifically reactive to WT-1 peptide was established and its cytotoxicity to leukemia cells was examined. This T cell clone showed cytotoxicity in an HLA-A*2402-restricted manner. The results of the study thus show that peptides derived from WT-1 are binding to the HLA-A*2402 molecules on leukemia cells, and support the

possibility of development of leukemia-specific immunotherapy using a peptide-specific CTL clone.

Problem and its solution

63. In view of this state of the art and in view of the effects achieved by the present invention - see the examples - the problem to be solved consists in the provision of alternative means for the therapy of cancer in a different population.
64. As the solution to this problem the patent proposes a peptide having a molecular weight of 5 000 or less comprising the amino acid sequence RMFPNAPYL, wherein the peptide includes non-peptide bonds. The peptide RMFPNAPYL binds HLA-A*0201, an HLA-A haplotype prevalent in the Caucasian population. In view of the experimental results reported in the patent (see paragraphs [0122] to [0132]) the board is satisfied that the technical problem is solved.

Obviousness

65. It remains to be decided whether or not the proposed solution is obvious in view of the prior art. For the benefit of appellant II, the board accepts that the skilled person, faced with the problem indicated above, would have been interested in the treatment of cancer in the Caucasian population and would thus have looked for a peptide binding to HLA-A*0201 which is one of the most common haplotypes in the Caucasian population. Document (D4) is silent as regards the possibility of synthesising peptides comprising binding motifs for HLA subtypes prevalent in different populations. Hence

- document (D4) alone does not render the claimed solution obvious.
66. The skilled person working in the field of immunotherapy of cancer and knowing document (D4) is however also aware of document (D5). Document (D5), a review article, provides a compendium of MHC peptide motifs and MHC ligands known in the year 1994. It discloses that the peptide motifs of many of the more important MHC class I molecules are known and that this information will be useful for the prediction of T-cell epitopes within proteins of known sequences. Document (D5) explains the basic approach to search a protein sequence for an epitope fitting to a given class I molecule as follows: First the sequence is screened for stretches fitting to the basic anchor motif which will lead to a list of candidates. These are then inspected for having as many non-anchor residues as possible in common with ligands already known or with the residues listed among the "preferred residues" or "others" on top of each motif Table. Finally, a binding assay can be performed to exclude weak binders which occur frequently among peptides conforming to a basic motif (see abstract, page 182, right hand column, fourth paragraph to page 183, left hand column, first paragraph).
67. The board has no doubt that a skilled person faced with the problem formulated above would go ahead and use the approach suggested in document (D5) and the information provided in the motif Table 2 on page 193 of the same document and thus identify in an obvious way potential HLA-A*0201 binding peptides in the WT-1 sequence.

68. However, not all of the peptides thus identified will necessarily be useful in cancer therapy. For this the peptide has not only to bind HLA-A*0201, it also has to be the peptide naturally processed and presented in the context of MHC class I on tumor cells. The board is not convinced by appellant II's argument that only routine methodology and diligence were required for the identification of the natural CTL epitope.
69. Indeed, document (D5) cautions that the identification of the natural ligand is not straightforward, see page 183, left hand column, first paragraph last sentence where it states that: *"One should keep in mind, however, that pure peptide binding motifs can be misleading in the search for natural ligands, since other constraints, such as enzyme specificity during antigen processing and specificity of transporters or chaperons, are likely to contribute to ligand identity in addition to the MHC binding specificity."*
70. The patent in suit used the following tumour cell lines for the identification of the natural CTL epitope: leukemia cell line BV173, the leukaemia cell line Leuk-697 and the breast cancer cell line MDA-MB231 (see Table bridging pages 11 and 12 of the patent).
71. There is evidence on file that shows that the choice of the tumor cell line used for the identification of the natural CTL epitope is crucial. Both parties relied in their argumentation on document (D2), an intermediate document, as technical evidence (see sections XIII and XIV above) and the board agrees that document (D2) can be considered as technical evidence in the present circumstances. Document (D2) discloses (see page 102)

that CTL lines were generated that showed peptide specific lysis, but only p130-138 (NAPYLPSCL) specific CTL showed lysis of a WT-1 positive tumor cells line, while p126-134 (RMFPNAPYL) specific CTL did not lyse a WT-1 positive tumor cell line. Document (D2) concludes that NAPYLPSCL but not RMFPNAPYL appears to be the naturally processed epitope. The board concludes that not all tumor cell lines would have led to the identification of the peptide RMFPNAPYL as the natural CTL epitope.

72. In the absence of any prior art that would have prompted the skilled person faced with the problem identified above to use the particular cell lines used in the patent in suit the board acknowledges an inventive step.
73. The board sees its decision to be in line with decision T 1396/06 of 31 May 2007 (reasons, point 37) in which the board (in a different composition) has held in a similar situation that *"it is not the theoretical possibility to isolate a substance by applying a known method, but the actual provision of one specific peptide for a defined use, not disclosed in the prior art, which establishes elements of surprise justifying acknowledgement of an inventive step"*.
74. The above considerations in respect of claim 1 of the main request apply *mutatis mutandis*, to the subject-matter of independent claims 3, 4, 5, 11, 14, 16 and 17 and to remaining dependent claims 2, 6 to 10, 12, 13, 15. The main request fulfils 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 department of first instance with the order to maintain the patent on the basis of the main request filed during the oral proceedings and a description and figures to be adapted thereto.

The Registrar:

The Chairman:

D. Hampe

C. Rennie-Smith

G. Alt

(as foreseen by Article 8(3) RPBA)