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**Datasheet for the decision  
of 29 September 2015**

**Case Number:** T 1734/10 - 3.3.04

**Application Number:** 99940722.4

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**IPC:** C07K14/435, A61K38/17,  
A61P35/00

**Language of the proceedings:** EN

**Title of invention:**

Peptides that elicit T cellular immunity

**Applicant:**

GemVax AS

**Headword:**

Frameshift peptide/GEMVAX

**Relevant legal provisions:**

EPC Art. 56, 83, 94(3), 111(1)

EPC R. 71(1)

RPBA Art. 11

**Keyword:**

Remittal to the department of first instance - (no)

Auxiliary request 1 to 11 - sufficiency of disclosure - (no)

Auxiliary request 12 - requirements of the EPC met - (yes)

**Decisions cited:**

T 0640/91, T 0951/92, T 1578/05, T 1237/07, T 0625/09,

T 0301/10, T 1500/10

**Catchword:**



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Case Number: T 1734/10 - 3.3.04

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.04**  
**of 29 September 2015**

**Appellant:** GemVax AS  
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**Decision under appeal:** **Decision of the Examining Division of the European Patent Office posted on 11 March 2010 refusing European patent application No. 99940722.4 pursuant to Article 97(2) EPC.**

**Composition of the Board:**

**Chairwoman** G. Alt  
**Members:** B. Claes  
L. Bühler

## Summary of Facts and Submissions

- I. The appeal lies from the decision of the examining division to refuse European patent application No. 99940722.4, which was published as WO 99/58552.
- II. During the proceedings before the examining division the applicant had requested oral proceedings in case the division was inclined to issue an adverse decision. Oral proceedings before the examining division took place on 25 November 2009 during which the applicant was not present nor represented.
- III. The impugned decision is based on a main request and first to fifth auxiliary requests, all filed on 19 November 2009. The subject-matter of claims 1 to 4 of the main request, claim 1 of the second and the third auxiliary requests and claims 1 to 4 of the fourth auxiliary request was found to contravene the requirements of Article 123(2) EPC. The subject-matter of claims 2 and 3 of the 5th auxiliary request was considered to lack novelty (Article 54(2) EPC). The first auxiliary request was not admitted into the proceedings pursuant to Rule 137(3) EPC.
- IV. With the statement of grounds of appeal, the appellant submitted ten claim requests and a main, procedural request that the case be remitted to the examining division with the order to issue a communication under Article 94(3) and Rule 71(1) EPC on the basis of the claims filed on 10 March 2008, and the description and drawings as originally filed.
- V. In a communication pursuant to Article 17(1) RPBA the board expressed its preliminary and non-binding opinion that, *inter alia*, the procedural request could not be

allowed and that all the claim requests on file contravened the requirements of Article 83 EPC.

VI. The appellant replied on 22 May 2015, re-submitted the procedural request as the main request and filed twelve auxiliary requests to replace all previously filed claim requests.

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

"1. A peptide that

a) is at least 8 amino acids long and is a fragment of a mutant protein arising from a frameshift mutation in the TGF- $\beta$ -RII gene in a cancer cell;

and

b) consists of at least one amino acid of the mutant part of a protein sequence encoded by said gene;

and

c) comprises 0-10 amino acids from the carboxyl terminus of the normal part of the protein sequence preceding the amino terminus of the mutant sequence and may further extend to the carboxyl terminus of the mutant part of the protein as determined by a new stop codon generated by the frameshift mutation;

and

d) induces, either in its full length or after processing by antigen presenting cell, T-cell responses;

characterised in that the mutant part of the protein has a sequence chosen from the sequences with the sequence identity nos 13-21 and 428,

for use as a medicament in the treatment of cancer in a person by administering at least one said peptide one or more times in an amount sufficient for induction of T-cell immunity to mutant TGF- $\beta$ -RII protein arising from said frameshift mutation."

Claim 1 of the **2nd to the 8th auxiliary requests** differed from claim 1 of the main request in that the mutant part of the protein:

- had a sequence chosen from SEQ ID NO: 13 and the amino acid sequence Ala-Trp (in the 2nd and 4th auxiliary requests), or
- had a sequence chosen from SEQ ID NOs: 13-21 and 428 and the peptide was 8-25, 9-20, 9-16, 8-12, 20-25, 9, 12 or 13 amino acids long (in the 5th and 7th auxiliary requests), or
- had a sequence chosen from SEQ ID NO: 13 and the amino acid sequence Ala-Trp and the peptide was 8-25, 9-20, 9-16, 8-12, 20-25, 9, 12 or 13 amino acids long (in the 6th and 8th auxiliary requests)

Moreover, in the 3rd, 4th, 7th and 8th auxiliary requests part b) of claim 1 had an additional feature (emphasis added below in bold by the board) which read: "consists of at least one amino acid of the mutant part of a protein sequence encoded by said gene **so that said fragment corresponds to a transformed TGF- $\beta$ -RII protein product from a frameshift mutation**".

Claim 1 of the **9th auxiliary request** read:

"1. A peptide that

a) is at least 8 amino acids long and is a fragment of a mutant protein arising from a frameshift mutation in the TGF- $\beta$ -RII gene in a cancer cell;

and

b) is selected from any one of SEQ ID NOs: 13-21 and 428 or is selected from a fragment of any one of SEQ ID NOs: 13-21 and 428, said fragment of any of SEQ ID NOs: 13-21 and 428 corresponding to a transformed TGF- $\beta$ -RII protein product arising from a frameshift mutation;

and

c) induces, either in its full length or after processing by antigen presenting cell, T-cell responses;

for use as a medicament in the treatment of cancer in a person by administering at least one said peptide one or more times in an amount sufficient for induction of T-cell immunity to mutant TGF- $\beta$ -RII protein arising from said frameshift mutation."

Claim 1 of the **10th auxiliary request** read:

"1. A peptide that

a) is at least 8 amino acids long and is a fragment of a mutant protein arising from a frameshift mutation in the TGF- $\beta$ -RII gene in a cancer cell;

and

b) is selected from any one of SEQ ID NOs: 13-21 and 428;

and

c) induces, either in its full length or after processing by antigen presenting cell, T-cell responses;

for use as a medicament in the treatment of cancer in a person by administering at least one said peptide one or more times in an amount sufficient for induction of T-cell immunity to mutant TGF- $\beta$ -RII protein arising from said frameshift mutation."

Claim 1 of the **11th auxiliary request** read:

"1. A peptide that

a) is at least 8 amino acids long and is a fragment of a mutant protein arising from a frameshift mutation in the TGF- $\beta$ -RII gene in a cancer cell;

and

b) comprises 0 amino acids from the carboxyl terminus of the normal part of the protein sequence preceding the amino terminus of the mutant sequence;

and

c) induces, either in its full length or after processing by antigen presenting cell, T-cell responses;



characterised in that the mutant part of the protein has SEQ ID NO: 17,

for use as a medicament in the treatment of cancer in a person by administering at least one said peptide one or more times in an amount sufficient for induction of T-cell immunity to mutant TGF- $\beta$ -RII protein arising from said frameshift mutation.

VIII. The independent claims of the **12th auxiliary request** (with claims 1 to 5) read:

"1. A peptide that has the amino acid sequence SEQ ID NO.17, for use as a medicament in the treatment of cancer in a person by administering at least one said peptide one or more times in an amount sufficient for induction of T-cell immunity to mutant TGF- $\beta$ -RII protein arising from said frameshift mutation.

2. A DNA sequence encoding a peptide as disclosed in either claim 1 for use as a medicament in the treatment of cancer in a person by administering at least one said DNA sequence one or more times in an amount sufficient for induction of T-cell immunity to mutant TGF- $\beta$ -RII protein arising from said frameshift mutation.

3. A vector (e.g. plasmid or virus vector) comprising a DNA sequence of claim 2 for use as a medicament in the treatment of cancer in a person by administering at least one said vector one or more times in an amount sufficient for induction of T-cell immunity to mutant TGF- $\beta$ -RII protein arising from said frameshift mutation.

5. Use of a peptide as defined in claim 1 or of a DNA sequence defined in claim 2 or of a vector as defined in claim 3 or 4, in the preparation of a pharmaceutical composition for treatment or prophylaxis of cancer in a person by administering said composition one or more times to the person in an amount sufficient for induction of T-cell immunity to mutant TGF- $\beta$ -RII protein arising from said frameshift mutation."
- IX. After receiving summons for oral proceedings, the appellant informed the board that it would not attend and relied on its written submissions.
- X. In a telephone conversation prior to the oral proceedings the rapporteur informed the appellant's representative that the board was of the preliminary opinion that the 12th auxiliary request filed with the letter dated 22 May 2015 complied with the requirements of the EPC.
- XI. Oral proceedings were held in the absence of the appellant. At the end, the chairwoman announced the decision of the board.
- XII. The following documents are cited in the decision:
- D16: WO 96/31605
- D18: Townsend *et al.* (1994), *Nature*, vol. 371, p. 662.

XIII. The appellant's arguments can be summarised as follows:

*Remittal to the examining division with the order to issue a communication under Article 94(3) and Rule 71(1) EPC on the basis of the claims filed on 10 March 2008*

By issuing summons to oral proceedings on 2 July 2009 instead of a communication pursuant to Article 94(3) EPC, the examining division had exercised its discretion to do so in an unreasonable way.

Article 94(3) EPC provides that the examining division must invite the applicant to file observations and amendments when it is necessary. In the annex to the summons the examining division introduced two newly cited documents and changed the reasoning underlying the existing objection of lack of inventive step. In addition, the annex contained an objection under Article 123(2) EPC to the claims filed on 10 March 2008. A communication according to Article 94(3) EPC would therefore have been necessary given these new facts introduced by the examining division. Absent such communication, the examining division failed to comply with the requirements of Article 94(3) EPC.

The existence of a conditional request for oral proceedings should not put the applicant in a worse situation than if such request had not been made. Oral proceedings were to be held as a last resort, when the examination procedure had come to a stand-still. This was however not the situation when the summons to oral proceedings were issued in the present case, where the two communications by the examining division had been responded with *bona fide* attempts to limit the claims

so as to provide a definition of patentable subject-matter.

*Sufficiency of disclosure (Article 83 EPC)*

TGF- $\beta$ -RII frameshift mutant proteins were foreign to the immune system and thus necessarily immunogenic in a proportion of individuals.

The data in the application could not give a meaningful overview over the claimed peptides' effects in a whole population, since the immunogenicity was shown in a small set of individuals. Due to the inter-individual differences in HLA types, the peptides shown to be immunogenic in the examples would not be expected to be effective in all patients, whereas it was equally likely that the peptides not found effective in the present examples would indeed be effective in individuals with a different HLA profile.

The superior effect of the peptide having SEQ ID NO: 17 was correlated with the fact that it was longer than other tested peptides, which allowed the binding of more T-cell epitopes of different HLA. Sufficiency of disclosure could however also be acknowledged with respect to other shorter peptides, which had most likely a different HLA binding profile.

*Inventive step (Article 56 EPC)*

The technical problem to be addressed was the provision of means for combating cancers characterised by expression by tumour cells of frameshift mutated TGF- $\beta$ -RII. The closest prior art was document D16, which suggested immunisation with full-length frameshift mutated TGF- $\beta$ -RII protein. The document failed however

to establish that such a vaccination was indeed effective against cancer.

Document D18 dealt with the use of peptides from frameshift-mutated proteins and disclosed experimental results concerning immunity in mice, but failed to demonstrate that the peptides were recognised by human T-cells.

In contrast to documents D16 and D18, the application disclosed that the peptides recited in the claims were processed and presented by HLA molecules in cancer patients and that these patients had raised a T-cell response against the peptides.

Neither document D16 nor D18 demonstrated that frameshift mutated peptides were immunogenic in humans. Being a highly unpredictable property, establishing whether a peptide induced T-cell immunogenicity required experimentation and could not simply be deduced from any of these documents. Hence, the skilled person starting from document D16 would have had no particular expectation of success to find a peptide with the required immunogenicity and according suitability as a cancer vaccine.

- XIV. The appellant requested in writing that the decision under appeal be set aside and that the case be remitted to the examining division with the order to issue a communication under Article 94(3) and Rule 71(1) EPC on the basis of the claims of the main request, filed on 10 March 2008, and the description and drawings as originally filed (main request), or, alternatively, that a patent be granted on the basis of the claims of one of the 1st to 12th auxiliary request filed with letter dated 22 May 2015.

## **Reasons for the Decision**

*Main request - Remittal to the examining division with the order to issue a communication under Article 94(3) and Rule 71(1) EPC on the basis of the claims filed on 10 March 2008*

1. Under Article 111(1) EPC and Article 11 RPBA a board shall remit a case to the examining division if fundamental deficiencies are apparent in the examination proceedings. The violation of the right to be heard is normally considered as a fundamental deficiency of first instance proceedings, and remittal is often ordered accordingly (see Case Law of the Boards of Appeal of the EPO, 7th edition 2013, IV.E. 7.4.1 and 7.4.2).
  
2. Article 94(3) EPC requires that the examining division offers the applicant the opportunity to file observations and amend the application in response to its observations "as often as necessary". Similarly Rule 71(1) EPC provides that the examining division shall invite the applicant to correct deficiencies and to amend the application, where appropriate. Accordingly, both Article 94(3) and Rule 71(1) EPC provide the examining division with the discretion to assess when such an opportunity is "necessary" and this discretion has to be exercised objectively in the light of the circumstances of the case (see e.g. decision T 301/10 of 2 August 2010, point 5.3).
  
3. The appellant argued that the examining division contravened Article 94(3) EPC because it failed to invite the applicant, in a situation where it was necessary, to submit observations or amend the

application. This necessity arose according to the appellant in the present case firstly from the fact that the annex accompanying the summons to oral proceedings referred to a new ground for not accepting the claims filed in response to the last communication (an objection under Article 123(2) EPC). And secondly, it arose from the fact that the examining division introduced two further documents and changed the reasoning underlying the existing objection of lack of inventive step.

3.1 The board considers that, following the logic of the first aspect of the appellant's argument, the filing of claims in response to a communication by the examining division which include added matter - infringing therefore the requirements of Article 123(2) EPC - would *a priori* prevent the examining division from summoning the applicant to oral proceedings, as such claims would *a fortiori* be objectionable for a "new" non-compliance with the EPC. The board considers therefore that such circumstances cannot establish a necessity for the examining division to invite the applicant to submit observations as provided for in Article 94(3) EPC.

3.2 In the second aspect of the appellant's argument, the board can understand that the introduction of two further documents and the shifting of the reasoning for lack of inventive step may have caused additional work for the appellant when preparing for oral proceedings. The relevant question to be addressed in relation to the appellant's procedural request is however whether or not the principles set out in Article 113(1) EPC were respected by the examining division. The board considers that this question is to be answered in the positive in the present case because the annex to the

summons to oral proceedings contained the grounds and evidence which eventually led to the finding of the subsequent decision. Moreover, it is noted that the right to present comments enshrined in Article 113(1) EPC is not restricted to observations submitted in writing but may be satisfied by way of conducting oral proceedings (see e.g. decision T 951/92, OJ EPO 1996, 53; point 3 (a)(vi) or decision T 1237/07 of 12 February 2008, point 3). In the present case, the appellant had ample time to comment on the grounds and evidence on which the contested decision is based. After having received the summons and its annex, the appellant took indeed the opportunity to present comments in writing (twice, in fact). Further arguments were not presented orally because the appellant chose not to be represented at the oral proceedings.

4. The appellant considered that its conditional request for oral proceedings (see section II) had put it in a worse situation, than if the request had not been submitted, *i.e.* the request had instigated the examining division to summon to oral proceedings rather than issue a further communication under Article 94(3) EPC. The appellant argued also that, in his view, oral proceedings should be a last resort when no other means of progress in the examination procedure appeared possible, but that this situation had not arisen when the examining division summoned the appellant to oral proceedings. Indeed, the two previous communications of the examining division had been responded to with *bona fide* attempts to limit the claims.

- 4.1 In the context of Article 116(1) EPC, the board notes that oral proceedings shall take place not only at the request of a party but also at the instance of the EPO if it considers this to be expedient (see also e.g.



decision T 1500/10 of 20 December 2012 point 3.4 or decision T 625/09 of 21 July 2010, point 2.8). Hence, already for this reason the appellant's argument that the conditional request for oral proceedings might have put it in a worse situation than if the request had not existed is not considered persuasive.

4.2 Evaluating whether oral proceedings are indeed expedient is part of the examining division's discretion, which is to be exercised taking into account the progress made in the examination proceedings. The board can however not concur that discretion is limited to a "last resort situation" as mentioned by the appellant. The Guidelines for Examination appropriately state that oral proceedings will normally be expedient if *"after an attempt at written clarification there are still questions or doubts which have a crucial bearing on the decision to be reached and which may be more efficiently or surely settled by oral discussion with the party..."* (see part E, chapter II, point 4 in the version November 2014). It can be derived from this passage that the main consideration in the instructions received by the examining division is procedural economy and certainly not the condition of a complete lack of progress in an examination procedure (last resort situation).

5. A board of appeal should only overrule a decision based on the exercise of a discretion if it comes to the conclusion either that the examining division had not exercised it in accordance with the right principles or that it exercised its discretion in an unreasonable way (see e.g. decision T 640/91, OJ 1994, 918, Headnote III, or decision T 1578/05 of 26 April 2005, point 5.2.1). For the reasons and considerations set out above, the board takes the view that the examining

division exercised its discretion correctly both with regard to the decision not to issue a further communication and the decision to summon to oral proceedings.

6. The board concludes that the appellant's right to be heard was not violated by the summons to oral proceedings issued by the examination division. Consequently, the appellant's main request cannot be allowed.

*1st auxiliary request - Sufficiency of disclosure*

7. When considering medical use claims, *i.e.* claims where a therapeutic application is claimed, then attaining the claimed therapeutic effect is a functional technical feature of the claims. As a consequence, under Article 83 EPC, unless this was already known to the skilled person at the priority date, the application must disclose the suitability of the agent referred to in the claim for the claimed therapeutic application. A pharmaceutical effect *in vitro* which directly and unambiguously reflects the therapeutic application or a clear and accepted relationship between the shown physiological activities and the disease may suffice to establish suitability (see also Case Law of the Boards of Appeal of the EPO, 7th edition 2013, section II.C.6.2).
8. The subject-matter of claim 1 is a peptide for use in the treatment of cancer by induction of T-cell immunity to frameshift-mutated TGF- $\beta$ -RII protein. The peptide is structurally characterised by features (a) to (c) and by reference to SEQ ID NOs: 13-21 and 428, and is functionally characterised by feature (d) (see section VI). Structurally claim 1 defines a very wide range of

peptides, encompassing also e.g. such embodiments having only one amino acid in common with the mutant part of a mutant TGF- $\beta$ -RII protein (see feature b)), *i.e.* as represented in the claim by the peptide having SEQ ID NOs: 13 to 21 or 428, which themselves are up to 34 amino acids long.

9. The application under consideration discloses a number of examples and experimental results in relation to the immunogenicity of a number of peptides designed on the basis of frameshift-mutated TGF- $\beta$ -RII protein. The following experimental data are of particular interest for the present case:

9.1 Figure 4 demonstrates that the capability of T-cells of a pancreatic cancer patient to recognise and proliferate to the peptide having SEQ ID NO: 21 is virtually non-existent, *i.e.* their activity is similar to when no peptide is present, whereas their activity in response to the peptide having SEQ ID NO: 17 is significant in this respect. This is so despite the fact that the two peptides (*i.e.* SEQ ID NO: 17 and SEQ ID NO: 21) have 8 contiguous amino acids in common and are both contained in the list of the most preferred embodiments of table 8 on page 21 of the application.

9.2 Similarly, the experiment which relates to Figure 8 demonstrates that two T-cell clones from a tumor biopsy reacted specifically with the peptide of SEQ ID NO: 17 whereas they lacked such reactivity to peptides having SEQ ID NOs: 15 and 18. Again, these three peptides share a considerable number of contiguous amino acids, *i.e.* 9, and the non-reactive peptides of SEQ ID NOs: 15 and 18 are also contained in the list of most preferred embodiments in Table 8 on page 21 of the application as filed.

10. The application does not provide evidence whether any vaccine prepared using any of the peptides referred to in the examples has an effect on tumour growth or tumour prevention. In this context, therefore, the demonstration of suitability of the claimed peptides for the claimed therapeutic application as required under Article 83 EPC ought to hinge on a demonstration of their immunogenicity. The board notes, however, that there is not always a direct correlation between immunogenicity and therapeutic anti-cancer effect of a given compound. Nevertheless, and for the sake of the argumentation under Article 83 EPC however, the board notes that, independently of the question whether or not in the present case the immunogenicity effect directly and unambiguously reflects the therapeutic application (cancer treatment), failing to demonstrate such an effect necessarily results in failing to demonstrate the suitability of the compound for the therapeutic application.
  
11. In the board's view it follows from the analysis of the experimental data (see points 9 to 9.2) that the application under consideration fails to demonstrate for the peptides of SEQ ID NOs: 15, 18 and 21 (as active agents mentioned as reference points in and preferred embodiments of claim 1), an effect, which possibly, directly and unambiguously, could reflect their suitability for the claimed therapeutic application and the disease to be treated (cancer) or could demonstrate its activity in a mechanism involved in that pathology (here T-cell immunity towards mutated cancerous cells).
  
12. Furthermore, the board considers that if the experimental data in the application do not enable the

skilled person to conclude that peptides sharing 8 or 9 amino acids with the mutant part of the TGF- $\beta$ -RII protein as represented by the peptide of SEQ ID NO: 17 are effective in inducing T-cell immunity towards cancer cells (see points 9 to 9.2), this is necessarily even more true for fragments sharing only one amino acid with this mutant part (see point 8 above) and accordingly there is even less reason to plausibly expect that they might be suitable as anti-cancer agents. In fact, the board considers that a link between active agent and the disease to be treated is plausibly established in the application **only** for the peptide of SEQ ID NO: 17 (see point 24 below).

13. The appellant argued that, due to inter-individual variation in HLA types, peptides shown to be immunogenic in the examples of the application would likely not be effective in all patients. By the same token, it was equally likely that the peptides not found effective in the examples of the application for treating cancer in certain individuals would be effective in other patients. Thus, due to the small set of individuals tested, it was not to be expected that the results disclosed in the application could give a meaningful overview about the peptides' real effects in a whole population. The negative results disclosed in the application for certain peptides could therefore not be used for calling into question the suitability of the peptides for cancer treatment.
  
14. Whereas the board can concur that a cancer vaccine based on a peptide for which immunogenicity may have been demonstrated, such as e.g. SEQ ID NO: 17, may not be effective in every potential patient treated with it, it notes that there has been no evidence submitted by the appellant to demonstrate that peptides, for

which no immunogenicity could be demonstrated in the patients tested in the application, are immunogenic in other patients, let alone effective in treating cancer in these patients.

15. The appellant's argument appears furthermore at odds with an argument put forward by the appellant in the context of inventive step, according to which T-cell immunogenicity is "highly unpredictable" (see pages 9 and 10 of the statement of grounds of appeal). Indeed, the board notes that this lack of predictability appears to be confirmed by the examples of the application, as explained in points 9 to 10 above. The board therefore finds the argument of the appellant not persuasive.
  
16. In summary, in view of the experimental evidence disclosed in the application under consideration, no physiological activity, *i.e.* the induction of T-cell immunity, has been demonstrated in the application for any of the peptides encompassed by claim 1 (with the exception of the peptide of SEQ ID NO: 17) which could possibly establish the suitability of the peptides of the mutant part of the TGF- $\beta$ -RII protein as defined in claim 1 for the therapeutic application of claim 1. Such activity was not known from the prior art either.
  
17. Accordingly, the application as filed fails to sufficiently disclose the claimed medical use as required by Article 83 EPC.

*2nd to 10th auxiliary requests - Sufficiency of disclosure*

18. The subject-matter of claim 1 of these requests is limited as compared to that of claim 1 of the 1st auxiliary request. Nevertheless, in the board's

judgement, the observations made in points 7 to 11 and the conclusion in points 16 and 17 apply *mutatis mutandis* to the application in the context of claim 1 of the 2nd to 10th auxiliary requests. Accordingly, the application does not sufficiently disclose the subject-matter of claim 1 of these requests contrary to the requirements of Article 83 EPC.

*11th auxiliary request - Sufficiency of disclosure*

19. As noted above (see point 12) the application provides evidence that the peptide having SEQ ID NO: 17 is immunogenic and therefore possibly suitable for providing a treatment for cancer. The active ingredient in the medical use defined in claim 1 is a peptide of at least 8 amino acids which is a fragment of a frameshift-mutated form of TGF- $\beta$ -RII protein from which the mutant part has SEQ ID NO: 17. One of the peptides encompassed by claim 1 is a peptide having SEQ ID NO: 15, which is not active (immunogenic) in view of the experimental results contained in Fig. 8 of the application as filed (see also point 9.2 above). Accordingly, the board considers that on the basis of the evidence for the peptide having SEQ ID NO: 17 no plausible predictions can be made on whether or not modifications of the peptide of SEQ ID NO: 17 falling within the ambit of claim 1 would demonstrate the desired effect.
20. Therefore the application as filed fails to sufficiently disclose the claimed medical use which is the subject-matter of claim 1 as required by Article 83 EPC.

*12th auxiliary request*

*Added matter and novelty*

21. The subject-matter of claims 1 and 5 has a basis on page 53, lines 24 to 30, and also in claim 17 when dependent on claim 12 of the application as filed. The subject-matter of claims 2 to 4 finds a basis on page 63, line 41 to page 64, line 2, and also in claims 28 to 32 of the application as filed. The board is therefore satisfied that the claims satisfy the requirements of Article 123(2) EPC.
  
22. The objection in the impugned decision relating to novelty concerned a claim encompassing the peptide of SEQ ID NO: 13 and it does therefore not apply to the 12th auxiliary request, in which the claims are restricted to the peptide having SEQ ID NO: 17. The board is satisfied that the subject-matter claimed in the 12th auxiliary request complies with the requirements of Article 54 EPC.

*Sufficiency of disclosure*

23. Claim 1 relates to the second medical use of a peptide that has the amino acid sequence SEQ ID NO: 17. The application under consideration demonstrates that this peptide is processed and presented by HLA molecules in cancer patients and that these patients harbour T-cells that recognize the peptide (see Fig. 8, 9 and 10). Furthermore, the immunogenic effects are explained on pages 51, line 30 to 54, line 2.
  
24. The board notes in this context that it has not been demonstrated in the application whether a vaccine prepared using the peptide having SEQ ID NO: 17 has



indeed any effect on tumour growth or tumour prevention. As also noted before in such context (see point 10 above) the board is aware that there is not always a direct correlation between immunogenicity and therapeutic anti-cancer effect of a given compound. However, the T-cell clones used in the experimentation for the application were obtained from tumour biopsies and according to the passage on page 53 in lines 18 to 22, the activated T-cells specific for the peptide of SEQ ID NO: 17 were capable of homing to the tumour tissue after activation. In view of these results the board can accept that the immunostimulation demonstrated by the pharmacological data on file with respect to the peptide of SEQ ID NO:17 render it plausible to the skilled person that such a vaccine will indeed be effective as claimed.

25. Hence, the board considers that the 12th auxiliary request satisfies the requirements of Article 83 EPC.

*Inventive step*

*Closest prior art*

26. The invention aims at providing a treatment for human cancers associated with frameshift mutations in the TGF- $\beta$ -RII gene. The frameshift-mutated TGF- $\beta$ -RII gene produces a receptor unable to bind TGF- $\beta$ . This eliminates the sensitivity for the signal for down-regulation of cell growth in cancer cells and thus allows further tumour progress. The new C-terminal amino acid sequence created by the frameshift mutation is foreign to the body and exists only in cells carrying the mutation, *i.e.* in tumor cells and their pre-malignant progenitors. Being foreign to the immune system of the carrier, these amino acid sequences may

be recognised by T-cells. The therapeutic approach of the invention is based on the administration of a peptide corresponding to a specific frameshift-mutated amino acid sequence (namely the peptide having SEQ ID NO: 17) which elicits T-cell immunity to the mutant TGF- $\beta$ -RII arising from the frameshift mutated gene in cancer cells (see page 1 of the application as filed, lines 7 to 11 and 25 to 27, and page 19, lines 4 to 22).

27. Both the examining division and the appellant considered document D16 to represent the closest prior art document. The board considers document D16 also to represent the closest prior art in relation to the more limited subject-matter of claim 1 of this request.
  
28. Document D16 reports that TGF- $\beta$  inhibits growth of multiple epithelial cell types and that loss of this negative regulation contributes to tumour development. Over 100 examples of colon cancers suffering mutations in the TGF- $\beta$  type II receptor had been identified (see page 9, lines 12 to 15). The mutations are presented as being useful in cancer detection, diagnosis, prognosis or therapy (see e.g. page 34, lines 5 to 8). The document refers *inter alia* to a method for diagnosis or prognosis of cancer by detection of the absence of function of the TGF- $\beta$ -RII in the cells of a patient, and the provision of immunogenic compositions which elicit antibodies specifically reactive with cells expressing mutant forms of TGF- $\beta$ -RII (see page 1, lines 17 to 18 and page 2, lines 11 to 21). Document D16 discloses several amino acid sequences which result from the frameshift mutation in the TGF- $\beta$ -RII gene in colon cancer cell lines, including also SEQ ID NO: 13 (which is denoted SEQ ID NO: 3 on page 30, line 1 of document D16), being one of peptides described as most

preferred embodiments in the context of the application under consideration (see page 21, Table 8).

29. Although several passages in document D16 refer to the frameshift mutant forms of TGF- $\beta$ -RII as being immunogenic (see e.g. page 2, lines 20 to 21, page 5, lines 23 to 27; page 24, lines 24 to 25 or claim 11), document D16 fails to demonstrate such immunogenicity for sequences based on such frameshift mutated gene (the examples concern only detection of various cancer types, not therapy). In fact, the teaching of document D16 is limited to the mere suggestion of a therapeutic approach which is similar to that of the application, but lacks information on how to identify a specific peptide effective for such approach. Indeed, as also held by the appellant, document D16 provides at most a general therapeutic approach and an incentive to investigate its feasibility.

*Technical problem to be solved and its solution*

30. Starting from the general teaching in document D16, the technical problem to be solved can be formulated as the provision of a peptide for the treatment of cancers associated with frameshift mutated TGF- $\beta$ -RII by immunotherapy.
31. As the solution to this problem, claim 1 proposes the use of the peptide having SEQ ID NO: 17. In view of the considerations in relation to sufficiency of disclosure (see point 24 above), the board is satisfied that the peptide of claim 1 solves the formulated problem.

*Obviousness*

32. It needs to be decided whether the skilled person faced with the technical problem formulated above, *i.e.* the provision of a peptide for the treatment of cancers associated with frameshift mutated TGF- $\beta$ -RII by immunotherapy, and starting from the teaching of document D16, would have arrived at the peptide having SEQ ID NO: 17 in an obvious manner.
  
33. It has been pointed out in a number of decisions of the boards of appeal in the field of biotechnology that, in evaluating the attitude of the skilled person, one should not confuse a "hope to succeed", which is linked to the wish that a result be achieved, with a "reasonable expectation of success", which implies the ability to reasonably predict, based on the particular technical circumstances, a successful conclusion of a project within acceptable time limits (see Case Law Book of the Boards of Appeal of the EPO, 7th edition 2013, I.D.7.1).
  
34. Cancer immunotherapy was an active field of research at the effective date of the application under consideration. For instance document D18 reports the *"mounting enthusiasm for the idea that antigens in malignant cells might be used as vaccines to induce tumour-specific cell-mediated immunity [...] [H]ere we suggest an additional, potentially powerful source of tumour antigens that may arise by frameshift mutations"* (see left-hand column, first and second paragraphs). However, at the relevant date, the skilled person had no practical experience with cancer vaccines based on this approach. Indeed document D18 also states that *"[M]uch work is required to establish the value of*

- these sequences as tumour vaccines"* (see middle column, first and second paragraphs).
35. The board is satisfied that the skilled person had the incentive to investigate the the feasibility of the general approach as suggested in document D16 (see points 27 and 28). In the board's view the skilled person would have readily undertaken, starting from the disclosure in document D16, to design peptides based on frameshift mutations from the TGF- $\beta$ -RII in the hope to succeed to identify one suitable for cancer immunotherapy. However, as noted in point 26 above, when starting from the mutations mentioned in document D16, the skilled person had no pointer towards any particular protein fragment which could serve as a starting point for the required *in vivo* testing of T-cell responses. Indeed the board agrees with the appellant's argument that *in vivo* immunogenicity cannot be predicted from a peptide's structure, and that the identification of peptides which are processed and presented by antigen presenting cells can only be established via experimentation.
36. Accordingly, in view of these considerations the board considers that the skilled person was in a position where it could not necessarily predict that the identification of a peptide effective for the treatment of cancers associated with frameshift-mutated TGF- $\beta$ -RII would be successful. Therefore the board judges that the skilled person did not have the reasonable expectation of success.
37. Hence, the subject-matter of claim 1 cannot be considered as being rendered obvious to the skilled person by the prior art and accordingly involves an inventive step.

38. Since the DNA sequence of claim 2 encodes the peptide of claim 1 and the vector of claims 3 and 4 comprises the DNA of claim 2, the reasons given above as to why the subject-matter of claim 1 involves an inventive step apply analogously also for the subject-matter of claims 2 to 4. These reasons apply equally to the subject-matter of the medical use of claim 5, relating to the same peptide as claim 1 (or DNA or vector of claims 2 to 4) but drafted in a "Swiss-type format".
39. Consequently, the subject-matter of claims 1 to 5 fulfills 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 examining division with the order to grant a patent on the basis of claims 1 to 5 filed as 12th auxiliary request with the letter dated 22 May 2015 and a description and drawings to be adapted thereto.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated