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Datasheet for the decision of 2 October 2018

Case Number: T 1433/14 - 3.3.04

Application Number: 02736514.7

Publication Number: 1419175

IPC: C07K14/005

Language of the proceedings: EN

Title of invention:
"Replikin" peptides and uses thereof

Patent Proprietor:
Bogoch, Samuel, Dr.
Bogoch, Elenore, S.

Opponent:
Janssen Vaccines & Prevention B.V.

Headword:
Peptide Influenza Vaccine/BOGOCH

Relevant legal provisions:
EPC Art. 56

Keyword:
Main and auxiliary requests I to III - Inventive step - (no)

Decisions cited:
T 0939/92

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1433/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 2 October 2018

Appellant: (Patent Proprietor 1)	Bogoch, Samuel, Dr. 46 East 91st Street New York, New York 10128 (US)
Appellant: (Patent Proprietor 2)	Bogoch, Elenore, S. 46 East 91st Street New York, New York 10128 (US)
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Respondent: (Opponent)	Janssen Vaccines & Prevention B.V. Archimedesweg 4 2333 CN Leiden (NL)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the opposition division of the European Patent Office posted on 28 April 2014 revoking European patent No. 1419175 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	A. Chakravarty
	L. Bühler

Summary of Facts and Submissions

I. An appeal was filed by the patent proprietors (appellants) against the decision of the opposition division to revoke European patent No. 1 419 175. The patent is based on European patent application No. 02 736 514.7, with the title "*Replikin*" *peptides and uses thereof*".

II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC), lack of an inventive step (Article 56 EPC) and lack of industrial applicability (Article 57 EPC) and under Article 100(b) EPC, for lack of sufficient disclosure of the invention.

III. In the decision under appeal, the opposition division held that the subject-matter of claims 9 and 10 of the patent as granted lacked novelty and the subject-matter of claims 1 and 3 of auxiliary request 1 lacked an inventive step. The opposition division used its discretion not to admit auxiliary requests 2 and 3 into the proceedings because claim 1 of these requests was identical to claim 1 of auxiliary request 1.

IV. With the statement of grounds of appeal, the appellants filed a set of claims corresponding to auxiliary request 1 considered by the opposition division as a main request and sets of claims of auxiliary requests I to III, filed for the first time in the appeal proceedings. Furthermore, documents D60 to D65 were submitted.

V. The opponent (respondent) replied to the statement of grounds of appeal, submitting arguments *inter alia* as

to why the subject-matter of claims 1 and 3 lacked an inventive step.

VI. The board issued a communication pursuant to Article 15(1) RPBA together with a summons to oral proceedings. In it the parties were informed *inter alia* that the board considered that the subject-matter of claims 1 to 8 and 11 to 13 of the main request was a product as such and that no claimed subject-matter was a medical use of the "Swiss-type" or a "use-limited" product, as provided for by Article 54(4) and (5) EPC.

VII. The appellants responded to the board's communication with a letter accompanied by auxiliary requests IV to VI.

VIII. Claim 1 of the main request reads:

"1. An isolated or synthesized H1N1 influenza virus "Replikin" peptide from a hemagglutinin protein wherein said peptide consists of 7 to 50 amino acids comprising (1) at least one lysine residue located six to ten residues from a second lysine residue; (2) at least one histidine residue; and (3) at least 6% lysine residues".

Claim 1 of auxiliary request I reads:

"1. An isolated or synthesized H1N1 influenza virus "Replikin" peptide from a hemagglutinin protein wherein said peptide consists of 7 to 50 amino acids comprising (1) at least one lysine residue located six to ten residues from a second lysine residue; (2) at least one histidine residue; and (3) at least 6% lysine residues, wherein said lysine and said histidine are key "Replikin" amino acids and wherein said key amino acids

create space between them and are located at the ends of said peptide".

Claim 1 of auxiliary request II reads:

"1. An isolated or synthesized H1N1 influenza virus "Replikin" peptide from a hemagglutinin protein wherein said peptide consists of 7 to 50 amino acids comprising (1) at least one lysine residue located six to ten residues from a second lysine residue; (2) at least one histidine residue; and (3) at least 6% lysine residues and wherein said peptide is selected from any one of the amino acid sequences of SEQ ID NO(s): 135-179, 181-207. and 209-229".

Claim 1 of auxiliary request III reads:

"1. An isolated or synthesized H1N1 influenza virus "Replikin" peptide from a hemagglutinin protein wherein said peptide consists of 7 to 50 amino acids comprising (1) at least one lysine residue located six to ten residues from a second lysine residue; (2) at least one histidine residue; and (3) at least 6% lysine residues and wherein said peptide has the the amino acid sequence of SEQ ID NO: 141".

* the underlined sections represent the differences between claim 1 of the main request and claim 1 of each auxiliary requests I to III, respectively.

Claim 1 of auxiliary request IV reads:

"1. An antibody that specifically binds to an isolated or synthesized H1N1 influenza virus "Replikin" peptide from a hemagglutinin protein, wherein said peptide consists of 7 to 50 amino acids comprising (1) at least

one lysine residue located six to ten residues from a second lysine residue; (2) at least one histidine residue; and (3) at least 6% lysine residues, for use in a method for treatment of the human or animal body by therapy, wherein said antibody is comprised in a composition and wherein said composition comprises a pharmaceutically acceptable carrier and/or adjuvant.

Claim 1 of auxiliary request V reads:

"1. An antibody that specifically binds to an isolated or synthesized H1N1 influenza virus "Replikin" peptide from a hemagglutinin protein, wherein said peptide consists of 7 to 50 amino acids comprising (1) at least one lysine residue located six to ten residues from a second lysine residue; (2) at least one histidine residue; and (3) at least 6% lysine residues; and wherein said peptide consists of any one of the amino acid sequences of SEQ ID NO(s): 135-179, 181-207, and 209-229, for use in a method for treatment of the human or animal body by therapy, wherein said antibody is comprised in a composition and wherein said composition comprises a pharmaceutically acceptable carrier and/or adjuvant".

Claim 1 of auxiliary request VI reads:

"1. An antibody that specifically binds to an isolated or synthesized H1N1 influenza virus "Replikin" peptide from a hemagglutinin protein, wherein said peptide consists of 7 to 50 amino acids comprising (1) at least one lysine residue located six to ten residues from a second lysine residue; (2) at least one histidine residue; and (3) at least 6% lysine residues; and wherein said peptide has the amino acid sequence of SEQ ID NO: 141, for use in a method for treatment of the

human or animal body by therapy, wherein said antibody is comprised in a composition and wherein said composition comprises a pharmaceutically acceptable carrier and/or adjuvant".

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

D4: Gelder, C.M. *et al.*, 1995, J. Virol., 69(12), 7497-7706.

D8: Gerhard, W. *et al.*, 1991, J. Virol., 65(1), 364-372.

Documents D11, D16, D17, D18, D23, D23a, D30, D44 to D57 and D60 to D65 are also mentioned, it is however not necessary to provide their bibliographic data here, as they played no part in reaching the decision.

X. The appellants' arguments, relevant to the decision, are summarised as follows:

Admissibility of auxiliary requests I to III - Article 12(4) RPBA

These requests were filed with the statement of grounds of appeal because in the procedure before the opposition division, the preliminary non-binding opinion issued on 18 October 2013 stated that the opposition division was minded to reject the opposition. Accordingly, the appellant had no motive at that time to file any auxiliary claim requests.

Furthermore, at the oral proceedings, the opposition division focused the discussion on the issue of plausibility when considering the topic of inventive

step. This was a surprise to the appellants, who were consequently not in a position to submit appropriate further claim requests until the reasons set out in the decision under appeal were available.

Admissibility of auxiliary requests IV to VI - Article 13 RPBA

Auxiliary requests IV to VI were filed in direct response to the objections first set out in the board's communication pursuant to Article 15(1) RPBA. There had been no opportunity to file such requests earlier. In fact the changes made addressed the board's opinion that the subject-matter of claims 4 to 8 and 11 to 13 was a product *per se* and not a medical use claim. Previous to this opinion of the board, all parties had had a different assumption. It followed that the amendments made did not represent an amendment to the case in the sense of Article 13(1) RPBA.

Main request and auxiliary requests I to III - claim 1 Inventive step - Article 56 EPC

The patent disclosed specific chemical structures that allowed targeting of the replication and survival function of H1N1 influenza virus strains, termed "Replikin" peptide sequences, being a sequence consisting of 7 to 50 amino acid residues, comprising at least 6% lysine residues, and having at least one lysine residue positioned six to ten residues from at least one other lysine residue and at least one histidine residue.

The patent in paragraphs [0031] and [0032] further disclosed that the inventors (i) took the H1N1 hemagglutinin amino acid sequences publicly available

in the PubMed database, (ii) visually scanned these amino acid sequences for the presence of the "Replikin" structure with defined ends, (iii) counted how often such a structure was found in a given hemagglutinin amino acid sequence and expressed these counts as counts per 100 amino acids of a given hemagglutinin amino acid sequence and (iv) linked this information to the year. Figure 7 also indicated that in total 390 H1N1 hemagglutinin sequences were analyzed (see upper right corner of Figure 7, H1N1 (N=390)).

The inventors had found a correlation between influenza epidemics or pandemics and the "Replikin" amino acid sequence count in hemagglutinin proteins, which was thus an indicator of these epidemics and pandemics.

Regarding the use of "Replikin" peptides as vaccines, the patent in paragraph [0079] stated "*The "Replikin" peptides of the invention, alone or in various combinations, are administered to a subject, preferably by i.v. or intramuscular injection, in order to stimulate the immune system of the subject to produce antibodies to the peptide*". Furthermore, "*Administration of Replikins stimulates the immune system to produce antibodies having a cytotoxic effect....* " (see paragraph [0052] of the patent) and "*An influenza peptide vaccine of the invention may include a single "Replikin" peptide sequence or may include a plurality of "Replikin" sequences observed in H1N1 influenza virus strains*" (see paragraph [0055] of the patent).

Table 4 of the patent provided 95 variable and non-variable "Replikin" sequences, present in H1 hemagglutinin proteins in isolates from the year 1918 through 2000. Thus, the patent provided at least 95

specific vaccine formulations against H1N1 virus strains.

That peptides comprising a "Replikin" could in general be successfully used for vaccination had been shown for the brain cancer cell derived peptide 'malignin' "*a 16-mer meeting all the requirements defined in paragraph [038] of the application underlying the present patent*" (see statement of grounds of appeal, point 5.41) which, when injected as a synthetic vaccine into rabbits, lead to abundant anti-malignin antibody production. The concentration of anti-malignin antibody in serum *in vivo* was shown to relate quantitatively to the survival of cancer patients and anti-malignin antibodies have been shown to be cytotoxic to cancer cells at a concentration of picograms (femtomolar) per cancer cell (see paragraph [0020] of the patent).

In summary, the structure-function relationship of a "Replikin" sequence in an H1 hemagglutinin protein from an H1N1 influenza virus was fundamental and thus each and every "Replikin" sequence present in an H1N1 virus-derived hemagglutinin could be used for vaccination.

In relation to the differences between the subject-matter of claim 1 of the main request and that of auxiliary requests I to III, the following was noted. Claim 1 of auxiliary request I made it clearer that the lysine and histidine amino acid residues were to be found at the either end of the claimed peptide. Claim 1 of auxiliary request II limited to claimed subject-matter to the specific peptides having one of sequences represented by SEQ ID NOs: 135 to 179, 181 to 207 and 209-229. Claim 1 of auxiliary request III further limited the claimed subject-matter to only one specific

33 amino acid long peptide, namely that having SEQ ID NO: 141.

Disclosure of the invention - Article 83 EPC

Regarding the suitability of the claimed antibodies for the claimed therapeutic use in the sense of Article 83 EPC, the arguments given on the topic inventive step for peptides claimed in the higher ranking requests applied *mutatis mutandis*.

XI. The respondent's arguments, relevant to the decision, are summarised as follows:

Admissibility of auxiliary requests I to III - Article 12(4) RPBA

Auxiliary requests I to III were filed on appeal and none corresponded to a previously filed claim request. Moreover, some of them were formally deficient. No explanations as to why these requests should be allowed into the proceedings was given and it was apparent from the minutes of oral proceedings before the opposition division that the appellant had not wished to file any further claim requests during the oral proceedings after the opposition division announced that auxiliary request 1 lacked an inventive step.

Furthermore, the amendments now proposed in auxiliary request I were based on the description rather than the granted claims and therefore complicated the case. The claims were however, analogous to those that the proprietor had filed before grant. This meant that this claim request could and should have been filed earlier. None of these requests should be admitted.

Admissibility of auxiliary requests IV to VI - Article 13 RPBA

These claim requests were filed in response to the board's preliminary opinion and were late filed. They should not be admitted into the proceedings since they could and should have been made earlier. Under Article 13 RPBA, the board had the discretion not to admit the requests and since the objections to the claimed subject-matter had been on file at least since the beginning of the appeal, there was no reason to submit these request only at this late stage.

Inventive step - Article 56 EPC
Main request and auxiliary requests I to III - claim 1

The alleged patentability of the claimed subject-matter was based on the idea that the appearance of a particular pattern of amino acids in influenza virus hemagglutinin proteins, termed a "Replikin" sequence motif, somehow correlates with the replicative activity of influenza strains, and that as a result:
(i) analyses of "Replikin" sequences can be used for the prediction of influenza epidemics or pandemics; and
(ii) "Replikin" peptides are especially suitable for use in vaccine compositions.

However, neither the predictive use of "Replikin" sequences nor their therapeutic use was plausible from the technical content of the patent or from the evidence published after the filing date of the patent and cited by the appellants.

As to the predictive use, it was not plausible from the technical content of the patent that the identification of a "Replikin" motif counts across populations of

hemagglutinin proteins from different H1N1 strains enabled the prediction of epidemic or pandemic strains of influenza virus. There was no evidence in the patent to establish that "Replikin" counts could actually be used to identify influenza H1N1 strains likely to become epidemic or pandemic.

The opposition division was therefore correct to conclude that the skilled person would not, after reading the patent, be in a position to determine which "Replikin" peptides would be useful for preventing epidemics or pandemics.

The use of "*each and every*" possible "Replikin" sequence from any hemagglutinin protein of any influenza H1N1 strain as a vaccine was simply not plausible. Certainly, the explanatory text in the patent regarding the supposed functions of "Replikin" sequences in "*survival and rapid replication*", did not render it plausible that any of the peptides covered by claim 1 of the main request was an effective vaccine, nor did it render it plausible that any of the peptides disclosed in Table 4 of the patent was an effective vaccine.

The testing of the 16-mer 'glioma' peptide of SEQ ID NO: 4, mentioned in paragraph [0020] of the patent, was of no help in making the activity of the claimed peptides as vaccines against influenza plausible because that peptide did not even contain the allegedly important pattern of terminal Lys and His residues and also because it was from an unrelated type of protein derived from a cancer cell line and was suggested for use in treating glioma, not influenza.

In summary, the patent only contained a speculative disclosure of a desirable therapeutic effect of treating or preventing influenza virus infections for a huge number of peptides but contained no credible technical teaching of the achievement of a therapeutic effect of any peptide. In view of this and considering inventive step by the problem and solution approach, the closest prior art for the subject-matter claim 1 of the main request should be a disclosure of short peptides derivable from influenza virus hemagglutinin proteins and document D4 or document D8 could reasonably be selected for this.

Document D4 disclosed a number of short influenza virus-derived hemagglutinin peptides (page 7497, right hand column, end of penultimate paragraph and Figure 1) which constituted an arbitrary series of 118 16-mers, overlapping by 11 residues, spanning the entire sequence of an influenza hemagglutinin protein derived from a combination of two H3N2 strains: A/Beijing/32/92 and A/Hong Kong/90; also referred to as X117. These peptides were made to identify epitopes recognised by T-cells. Document D4 suggested that these experiments could be useful in the development of cross reactive T-cell vaccines against influenza virus infection (see the end of the abstract and the end of the discussion section in document D4).

None of the peptides in document D4 was derived from a H1N1 virus-derived hemagglutinin, and therefore the difference between these and the subject-matter of claim 1 of the main request lay in the serotype of the influenza virus the hemagglutinin peptides were derived from.

There was no credible evidence on file of any useful technical effect for the claimed H1N1 virus-derived hemagglutinin peptides vis-à-vis the H3N2-derived peptides disclosed in document D4, for either claim 1 or claim 2 of the main request. Furthermore, a number of the H3N2 peptides in document D4 contained the allegedly special pattern of amino acids recited in claim 1 of the main request.

In the absence of any evidence of a useful technical effect for the claimed peptides vis-à-vis the peptides disclosed in document D4, the peptides of claims 1 and 2 of the main request were arbitrary, alternative peptides, from H1N1 strains rather than H3N2 strains. The objective technical problem was therefore the provision of alternative influenza hemagglutinin peptides.

An inventive step could not be acknowledged for an arbitrary set of short H1N1 virus-derived hemagglutinin peptides, when it was obvious to the skilled person to make and test short peptides from the hemagglutinin protein of H1N1 viruses. The skilled person would have known that there were only three types of hemagglutinin found in human influenza viruses (H1, H2 and H3, see e.g. D2 at column 1) and indeed document D4 itself also referred to H1 and H2 types (page 7497, left hand column and page 7501, right hand column).

The skilled person would have arrived at the claimed peptides simply by applying the method disclosed in document D4 to the hemagglutinin protein of any H1N1 strain.

The antibodies of claim 3 of the main request lacked inventive step for the same reasons, i.e. they were

antibodies recognising peptides which were the result of an arbitrary, and thus obvious, selection of peptides.

Auxiliary requests II and III - claim 1

Claim 1 of auxiliary request II was directed to a subset of the peptides of the main request while claim 1 of auxiliary request III was directed to a peptide comprising SEQ ID NO: 141. Claim 1 of both auxiliary requests II and III contained the language that the claimed peptide "consists of 7 to 50 amino acids". It was therefore clear that the claimed subject-matter was not limited to the peptides consisting of the listed SEQ ID Nos but included peptides comprising these.

The limitation of the claimed subject-matter with respect to the main request did not affect the considerations on obviousness. The claimed subject-matter lacked inventive step for the same reasons as the main request.

Post-filing data contained in documents D30 and D55 could not be relied on to justify an inventive step of the subject-matter of claim 1 of auxiliary request III because it was not plausible from the technical content of the patent that any "Replikin" peptide (including a peptide comprising or consisting of SEQ ID NO: 141) solved any useful technical problem.

Auxiliary requests IV to VI - claim 1

Regarding the suitability of the claimed antibodies for the claimed therapeutic use in the sense of Article 83 EPC, the arguments given on the topic

inventive step for the peptides claimed in the higher ranking requests applied *mutatis mutandis*.

XII. Oral proceedings before the board were held on 2 October 2018, both parties being represented. At the end of these proceedings the Chair announced the decision of the board.

XIII. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the main request or on the basis of the claims of one of auxiliary requests I to III, filed with the statement setting out the grounds of appeal, or on the basis of the claims of one of auxiliary requests IV to VI, filed with letter dated 14 September 2018.

XIV. The respondent requested that the appeal be dismissed and further requested that auxiliary requests I to VI and documents D44 to D57 and documents D60 to D65 not be admitted into the appeal proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Admission of documents D44 to D57 and D60 to D65 into the proceedings - Article 13(1) RPBA

2. None of the above mentioned documents were relied on by the board in reaching its decision and they were not referred to by the parties in their relevant submissions. Consequently, the board did not decide on the admission of these documents.

Admission of auxiliary requests I to III into the proceedings - Article 12(4) RPBA

3. The board has the power to hold inadmissible facts, evidence or requests which could have been presented or were not admitted in the first instance proceedings (Article 12(4) RPBA). Auxiliary requests I to III were all filed with the statement of grounds of appeal. The board is persuaded by the appellant's arguments that they could not have filed them in the first instance proceedings because they were not prepared for the focus on plausibility in the context of the discussion of inventive step, in view of the fact that this topic was not mentioned in the summons to oral proceedings. The board therefore decided to admit these requests.

Admission of auxiliary requests IV to VI into the proceedings - Article 13 RPBA

4. With respect to auxiliary requests IV to VI, it is noted that, as submitted by the appellant, the amendments made include a change of claim 1 to a "medical use" format. Claim 1 of each of these requests is no longer for a product *per se* but instead for a "purpose-limited" product as provided for by Article 54(4) EPC. The board notes that, indeed, both parties had made submissions in the appeal on the basis that the requests included claims to a "medical-use" (see e.g. the respondent's reply to the appellants' statement of grounds of appeal, paragraph 4.1). Thus, the amendments made cannot be considered to represent an amendment to the case and their admission is not subject to the board's discretion. Auxiliary requests IV to VI are therefore in the appeal proceedings.

Main request and auxiliary requests I to III - claim 1

5. Claim 1 of auxiliary request III is for a peptide which "has" the amino acid sequence of SEQ ID NO: 141 (His Gln Asn Xaa Gln Gly Ser Gly Tyr Ala Ala Asp Gln Lys Ser Thr Gln Asn Ala Ile Xaa Gly Ile Thr Asn Lys Val Asn Ser Val Ile Glu Lys - where Xaa stands for any amino acid). The claim further states that the peptide is an "isolated or synthesized H1N1 influenza virus Replikin peptide from a hemagglutinin protein wherein said peptide consists of 7 to 50 amino acids comprising (1) at least one lysine residue located six to ten residues from a second lysine residue; (2) at least one histidine residue; and (3) at least 6% lysine residues".

6. There was disagreement between the parties about whether or not the claim was for a peptide consisting of SEQ ID NO: 141 (i.e. a 33 amino acid long peptide) or whether it also encompassed longer sequences, comprising said sequence in its scope. However, regardless of which of these approaches to claim construction is taken, it is common ground that the claim encompasses a peptide consisting of SEQ ID NO: 141.

7. The following considerations concern a peptide consisting of SEQ ID NO: 141 and affect all claims encompassing this peptide, either as the sole subject-matter or as an embodiment.

Inventive step - Article 56 EPC

8. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal apply the "problem and solution" approach.

9. This approach involves (a) identifying the "closest prior art" by taking into account the general purpose of the invention, (b) assessing the difference between the closest prior art and the claimed invention and determining the technical effects of that difference, (c) defining the technical problem as one which aims at achieving these effects and, finally, (d) determining whether or not the skilled person would have considered the claimed subject-matter as an obvious solution to this technical problem, having regard to the state of the art within the meaning of Article 54(2) EPC.

10. Thus, one step of the "problem and solution" approach is the determination of the technical effect of the invention in relation to the closest prior art. This effect is then taken into account when formulating the objective technical problem. It is determined on the basis of the disclosure in the patent application or patent and takes into account whether or not the effect is achieved by substantially all embodiments of the claimed subject-matter, to ensure that claimed subject-matter can be considered as representing a solution to this problem as being solved by the claimed subject-matter (see decision T 939/92, reasons 2.6).

11. It is also established practice of the boards to begin the assessment of inventive step with the technical effect/technical problem ascribed to the claimed subject-matter in the patent application or the patent. However, if it becomes apparent that a purported technical effect is not achieved by all of the claimed subject-matter, for instance because it is not plausible that the claimed subject-matter actually achieves the purported effect (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition, I.D.4.2), then the problem cannot be

considered as having been solved (see point 10. above). In such a case the technical problem is reformulated in a less ambitious way and the obviousness of the claimed solution to that reformulated problem in the light of the cited prior art is assessed (*Id.*, I.D.4.4.1).

12. In the present case, the appellants argued that the peptide of claim 1 has the technical effect that it could be used as a vaccine against H1N1 influenza virus infection, as supported by the disclosure in the application in the following ways:

i) a sequence motif consisting of 7 to 50 amino acids comprising (1) at least one lysine residue located six to ten residues from a second lysine residue; (2) at least one histidine residue; and (3) at least 6% lysine residues which was termed a "Replikin" was identified (see paragraph [0005] of the patent).

ii) the "Replikin" count in H1 hemagglutinin proteins was correlated to the occurrence of influenza epidemics and pandemics and thus an indicator of these epidemics and pandemics (see paragraph [0032] of the patent). Table 4 listed the H1N1 virus-derived hemagglutinin "Replikin" sequences in order of frequency of occurrence, i.e. those found in viruses in more years were higher in the table.

iii) the peptide "SEQ ID NO: 141" was in the seventh position in Table 4, which showed that it was very likely to be useful as a protective vaccine.

iv) the general usefulness of peptides comprising a "Replikin" sequence for vaccination was demonstrated by the brain cancer cell-derived peptide malignin, having

the sequence "YKAGVAFLHKKNDIDE" (see paragraph [0020] of the patent).

v) the fundamental structure-function relationship of a "Replikin" sequence of an H1N1 virus-derived hemagglutinin protein was such that each and every hemagglutinin Replikin" sequence which was H1N1 virus-derived could be used for vaccination (see paragraph [0074] of the patent).

13. The board is not persuaded that the skilled person, when reading these disclosures in the light of the common general knowledge in the art, would consider it plausible that the peptide of claim 1 can be used as a vaccine at all and in particular, as a vaccine against H1N1 influenza virus infection.

13.1 In fact, at paragraph [0030], the patent discloses that the "Replikin" amino acid sequence count or concentration in the hemagglutinin protein may be correlated to influenza epidemics and pandemics and thus act as an indicator of these and pandemics. This is also true for the peptide of SEQ ID NO: 141, since Table 4 lists individual peptides according to the frequency of their occurrence in influenza epidemic years.

14. However, there is no evidence either in the patent or in the state of the art that there is a link between the above mentioned disclosure and the ability of any "Replikin" peptide to act as a vaccine against influenza virus infection. The disclosure in Table 4 of the high number of epidemic years in which SEQ ID NO: 141 occurs in the virus hemagglutinin protein is of no relevance to the assessment of whether or not it can elicit a protective immune response to

influenza virus, i.e. be useful as a vaccine, as there is no evidence, either in the patent or in the state of art, linking the two.

15. Indeed, the patent itself contains no evidence of any kind, in the form of results from either *in vivo* or *in vitro* experiments or otherwise to show that any "Replikin" peptide, and in particular a peptide of SEQ ID NO: 141, is capable of acting as a vaccine against H1N1 influenza virus.

16. The fact that the so-called malignin peptide of the sequence "YKAGVAFLHKKNDIDE", derived from a brain cancer protein, is able to elicit antibodies in rabbit and that these are cytotoxic to cancer cells *in vitro* (see paragraph [0020] of the patent) would not be considered generalisable to the present case by the skilled person, since this evidence relates to a different disease (cancer) and a different immunogen (i.e. the peptide differs from SEQ ID NO: 141).

17. The board has also seen no evidence that would allow it to conclude that the skilled person at the relevant date of the patent would have known on the basis of his common general knowledge that "Replikin" peptides in general could elicit protective immunity against any pathogen at all.

18. Finally, the assertion that the structure-function relationship between "Replikin" sequences in the H1N1 hemagglutinin protein means that each and every H1N1 "Replikin" sequence present in an H1N1 hemagglutinin can be used for vaccination is unsupported by evidence.

19. In view of the above considerations, the board concludes that at the relevant date of the patent, the

skilled person would not have considered it credible that the peptide of SEQ ID NO: 141 could be used as a vaccine against any influenza virus and H1N1 influenza virus in particular.

20. In accordance with the established jurisprudence of the boards of appeal, the assessment of inventive step is to be made at the effective date of the patent on the basis of the information in the patent together with the common general knowledge then available to the skilled person. That is to say that "*post-published evidence to support that the claimed subject-matter solves the problem to be solved is taken into account if it is already credible from the disclosure in the patent that the problem is indeed solved*" (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition, I.D.4.6).

21. In view of the conclusion in paragraph 19. above, the evidence in post-published documents D11, D16, D17, D18, D23, D23a, D29, D30, D47, D55 and D56, all submitted to show that the claimed subject-matter indeed has the technical effect ascribed to it in the patent, cannot be taken into account in the assessment of inventive step.

22. As a consequence, the technical problem must be reformulated in a less ambitious way taking into account a technical effect that is achieved by the claimed subject-matter (see point 11. above).

23. In the board's view a properly formulated problem is arrived at by applying the problem and solution approach (see point 9. above) in the following way.

24. As concerns the closest prior art, the skilled person would have known of peptides derived from the hemagglutinin protein of a type H3 influenza A virus for instance from document D4 (see abstract). This document discloses a series of 16-mer peptides spanning the entire sequence of an influenza hemagglutinin protein derived from a combination of two H3N2 strains, A/Beijing/32/92 and A/Hong Kong/90, and made for the purpose of identifying epitopes recognised by T cells, and finally for the development of cross reactive T-cell vaccines for influenza virus infection. A number of the peptides disclosed also comprise the "Replikin" sequence motif.

25. In view of this, the peptides disclosed in document D4 can be taken as representing the closest prior art for the claimed peptide.

26. Given that SEQ ID NO: 141 derives from the H1 hemagglutinin protein, the difference between the mentioned general knowledge of the above skilled person representing the closest prior art and the peptide claimed lies in its primary structure, i.e. its particular sequence, which is dictated by the sequence of the H1 type hemagglutinin and its length, i.e. it has 33 amino acids, compared to 16 amino acids. The board has seen no evidence that these structural differences manifest themselves in any technical effect other then the peptide being immunogenic.

27. In view of this difference and the associated technical effect, the problem to be solved by the claimed subject-matter is formulated as the provision of a further immunogenic peptide from a influenza A virus hemagglutinin protein.

28. The board has the following considerations about the obviousness of the claimed 33 amino acid long peptide represented by SEQ ID No. 141. It was generally known in the art that immunogenicity is a property shared by peptides in general, including those derived from the influenza A virus hemagglutinin proteins. Indeed, it was commonly known that very short peptides are less likely to be immunogenic than longer ones, which is reflected in document D4, where 16-mer peptides were chosen to map the T-cell epitopes of hemagglutinin from an H3N2 strain of influenza virus. As to choosing a peptide derived from a H1 hemagglutinin protein instead of one from an H3 hemagglutinin protein, the skilled person knew that the four prevalent strains of influenza virus contained H1 type hemagglutinin (see e.g. the patent at paragraph [30] and document D2 at column 1). This alone would have provided an incentive to seek immunogenic peptides from this protein. Thus, concentrating on a hemagglutinin type H1 was obvious to the skilled person.

29. The person skilled in the art, seeking to identify immunogenic peptides derived from a haemagglutination type H1 protein would, on the basis of the knowledge that peptides in general and those derived from haemagglutination in particular are immunogenic (see document D4, page 7501, right-hand column, final paragraph and document D8, abstract), would have considered that any peptide derived from that protein, and especially those of 16 or more amino acids in length, including the peptide consisting of SEQ ID NO: 141, would have provided equally suited solutions to the formulated technical problem.

30. It is established case law that in such a situation, arbitrarily selecting one these equally suitable

solutions is considered as obvious (see Case law of the Boards of Appeal of the European Patent Office, 8th edition, I.D.9.18.7). The board sees no reason to deviate from this case law.

31. Hence, the board comes to the conclusion that the claimed subject-matter does not meet the requirements of Article 56 EPC.

32. The above finding of obviousness applies equally to the subject-matter of claim 1 of all higher ranking requests (i.e. the main and auxiliary requests I and II) because the subject-matter of claim 1 of auxiliary request III is an embodiment of claim 1 of each of these requests.

Disclosure of the invention - Article 83 EPC
Auxiliary requests IV to VI - claim 1

33. The subject-matter of claim 1 of each of auxiliary requests IV and VI is an antibody for use in therapy of the human or animal body and is thus, a "use-limited" product, as provided for by Article 54(4) EPC.

34. The requirements of Article 83 EPC are complied with if the patent discloses the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. In the present case this means that the skilled person at the relevant date of the application should be able to make the claimed antibody and in the light of case law, the patent must disclose its suitability for a therapeutic application, i.e. for a medical use (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition, II.C.6.2).

35. As to the suitability of the claimed antibodies for the therapeutic application, the only therapeutic application of the claimed antibodies mentioned in the patent is the prevention or treatment of patients influenza virus infection (see paragraph [0083]). The board decided in point 19. above, that at the relevant date of the patent, the skilled person, reading the application and taking into account the general knowledge in the art, would not have considered it credible that the peptide of SEQ ID NO: 141 could be used as a vaccine against H1N1 influenza. This conclusion must apply equally to the antibodies of claim 1 of auxiliary requests IV to VI since these are the antibodies that are elicited by the peptide having SEQ ID NO: 141. Hence, the patent does not disclose the suitability of antibodies raised against the peptide of SEQ ID NO: 141 for the claimed therapeutic application.

36. It follows that claim 1 of each of the above requests does not meet the requirements of Article 83 EPC.

37. No claim request is allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

S. Lichtenvort G. Alt

Decision electronically authenticated