Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 13 February 2023

Case Number: T 0441/20 - 3.3.04

Application Number: 15188497.0

Publication Number: 3009145

IPC: A61K39/145, C07K14/11

Language of the proceedings: EN

Title of invention:
Influenza virus vaccines and uses thereof

Applicant:
Icahn School of Medicine at Mount Sinai

Headword:
Influenza vaccine/MOUNT SINAI

Relevant legal provisions:
EPC Art. 56, 84, 111(1)

Keyword:
Inventive step - in view of documents D1 to D4 (yes)
Appeal decision - remittal to the department of first instance (yes)

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0441/20 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 13 February 2023

Appellant: (Applicant)	Icahn School of Medicine at Mount Sinai One Gustave L. Levy Place New York, NY 10029 (US)
Representative:	Jones Day Rechtsanwälte, Attorneys-at-Law, Patentanwälte Prinzregentenstrasse 11 80538 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 21 August 2019 refusing European patent application No. 15188497.0 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairman	W. Sekretaruk
Members:	O. Lechner
	S. Albrecht

Summary of Facts and Submissions

I. The appeal of the applicant ("the appellant") is based on the decision of the examining division to refuse European patent application No. 15188497.0 ("the application"). The application and the invention to which it relates were found not to meet the requirements of the EPC (Article 97(2) EPC).

II. In the decision under appeal, the examining division decided to refuse the application on the grounds that neither the main request nor auxiliary request 1 was clear (Article 84 EPC) and neither of them involved an inventive step (Article 56 EPC).

III. With the statement of grounds of appeal, the appellant re-filed the sets of claims of the main request and auxiliary request 1 underlying the impugned decision together with arguments as to why these requests did comply with the requirements of the EPC.

IV. The board summoned the appellant to oral proceedings as requested and informed it of its preliminary opinion in a communication pursuant to Article 15(1) RPBA 2020.

In its preliminary opinion, the board referred to two documents, D9 and D10, which had been cited in proceedings before other national offices and which appeared to be highly relevant for the assessment of inventive step. Given that it was not evident whether or not the examining division had taken into account documents D9 and D10 in its examination of the application, the board indicated that it considered it appropriate to remit the case to the examining division for further prosecution. The appellant was invited to comment on the proposed course of action.

V. In a letter dated 17 January 2023, the appellant expressed its agreement with the board's proposal to remit the case to the examining division for the consideration of the prior art (D9 and D10) identified in section 15 of the board's communication under Article 15(1) RPBA 2020.

VI. Subsequently, the board cancelled the oral proceedings and announced that the appeal procedure would be continued in writing.

VII. The following documents are cited in this decision:

D1 : Gerhard *et al.*, Emerging Infectious Diseases (2006), 12(4): pages 569-574

D2 : Horváth *et al.*, Immunology Letters (1998), 60(2-3): pages 127-136

D3 : Bianchi *et al.*, Journal of Virology (2005), 79(12): pages 7380-7388

D4 : Mok *et al.*, Vaccine (2008), 36(37): pages 4775-4782

D9 : Sagawa H. *et al.*; Journal of General Virology (1996), 77: pages 1483-1487

D10: US 2002/0054882 A1

VIII. Claim 1 of the main request reads as follows:

"1. A polypeptide comprising:
a. an influenza A virus hemagglutinin HA1 domain that comprises an HA1 N-terminal stem segment

covalently linked to a linker of 1 to 50 heterologous residues that is in turn covalently linked to an HA1 C-terminal stem segment;
said HA1 domain being in tertiary association with

b. an influenza A virus hemagglutinin HA2 domain;

wherein the linker lacks a globular head domain;
wherein the HA1 N-terminal stem segment consists of amino acid residues A_{N-term} through A_p of the influenza A virus HA1 domain, wherein A_{N-term} is the N-terminal amino acid of a mature HA0 protein lacking a signal peptide, and wherein A_p is Cys that corresponds to amino acid position 52 of an HA1 domain using H3 numbering;
and
wherein the HA1 C-terminal stem segment consists of amino acid residues A_q through A_{C-term} of the influenza A virus HA1 domain, wherein A_q is Cys that corresponds to amino acid position 277 of an HA1 domain using H3 numbering, and wherein A_{C-term} is the C-terminal amino acid of the HA1 domain."

IX. The appellant's arguments, relevant to the decision, are summarised as follows:

(a) Article 84 EPC; claim construction

Claim 1 defined essential elements of the polypeptide of the invention, which were two influenza A virus HA1 stem domains linked by a linker and an influenza A virus HA2 domain. The claim expressly required that "the linker lacks a globular head domain". Given the clear wording of the claim and in view of the specification and the examples, the skilled person would readily appreciate that the linker did not contain a globular head domain.

The use of the word "comprising" in the preamble of the claim did not change this understanding. In fact, a different understanding would run contrary to the explicit wording of the claim. Moreover, replacing the word "comprising" by "consisting of" would unduly limit the protection conferred.

(b) Inventive step - Article 56 EPC

Closest prior art

The appellant started from document D1 as the closest prior art.

Difference, technical effect and objective technical problem to be solved

The difference between the closest prior art and the claimed subject-matter was that the vaccine candidates of document D1 were based on conserved and dominant viral determinants of M2 and the HA0 cleavage site of influenza A and B.

Vaccination with a "headless" influenza virus HA polypeptide of the claimed invention induced antibodies that were cross-reactive against heterologous influenza virus strains of the same subtype as the vaccine's "headless" influenza virus HA polypeptide (see, for example, paragraph [00409] and Figure 15 of the application as filed), whereas vaccination with the full-length influenza virus HA did not show, or showed only a low degree of, cross-reactivity to heterologous strains (see, for example, paragraph [00409], Figure 15B, 4th panel; Figure 15C, 4th panel, of the application as filed).

The objective technical problem could be seen as the provision of an improved vaccine that can be used to generate an immune response against multiple influenza strains.

The application provided sufficient information that demonstrated that the headless vaccine of the claimed invention had a broad protective activity, and therefore the objective technical problem of the invention was plausibly solved.

Obviousness

None of documents D1, D2 or D3 pointed in the direction of the claimed invention and none of these documents suggested the skilled artisan should modify the influenza HA protein by deleting the globular head region.
The vaccine candidates proposed in documents D1 to D3 were based on short peptides from a highly conserved HA0 cleavage site. Various ways to optimise these peptide-based vaccines were indicated in documents D1 to D3:

- Document D1 searched for alternative peptides from further conserved HA regions.
- Document D2 disclosed multimerisation of HA-derived peptides and their fusion with other HA-derived peptides.
- Document D3 provided combinations of HA peptides with various adjuvants and carrier proteins.

Furthermore, the skilled person would not have combined the teaching of document D4 with any of the teachings of documents D1 to D3. Document D4 taught that cellular responses could be induced from the subdominant

epitopes of the M2 protein of respiratory syncytial virus (RSV). There was no motivation for the skilled person to specifically apply the teaching regarding the RSV matrix protein 2 (M2 protein) to the HA protein of influenza A virus. The RSV M2 protein was not only functionally but also structurally distinct from the HA protein of influenza A virus. Moreover, document D4 specifically focused on CD8+ T cell responses to subdominant epitopes and emphasised the significance of the T cell response in RSV infection rather than B cell-mediated antibody responses, which was the relevant immune response to look for in the case of influenza HA.

In sum, none of documents D1 to D4 alone or in combination provided any conclusive evidence that taught, suggested or hinted at the possibility of generating the claimed polypeptides, not to mention any prospects of using said polypeptides for vaccination purposes against influenza A virus.

X. The appellant requested

- that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the main request filed by letter dated 24 June 2019 and re-filed with the statement of grounds of appeal, or, alternatively, on the basis of the set of claims of auxiliary request 1 filed with the same letter and re-filed with the statement of grounds of appeal.

Reasons for the Decision

Main request & auxiliary request 1

1. Article 84 EPC; claim construction

1.1 Claim 1 of each of these two requests is directed to a polypeptide comprising a specified influenza A virus haemagglutinin HA1 domain and an influenza A virus haemagglutinin HA2 domain. The recited HA1 domain includes a linker, wherein this linker lacks a globular head domain.

1.2 The examining division considered the term "globular head domain" as recited in claim 1 to be unclear. The board does not agree. As explained in section 16 of the impugned decision, the term "globular head domain" as recited in claim 1 is the globular head domain in its entirety, i.e. the entire amino acid sequence forming this domain. As a consequence, the linker of claim 1 may comprise parts of this sequence, such as immunodominant regions of the globular head domain.

1.3 The board does agree with the examining division that due to the use of the wording "comprising" in claim 1, the recited HA1 and HA2 domains must be "comprise[d]" in the claimed polypeptide, but further elements may also be present, such as immunodominant regions derived from the globular head domain in the linker (see section1.2 above) or elsewhere in the claimed polypeptide.

Contrary to the appellant's argumentation, the board is of the opinion that even the full globular head domain may be present in the claimed polypeptide, albeit outside the linker.

2. Inventive step - Article 56 EPC - in view of documents D1 to D4

Closest prior art

2.1 The board agrees that document D1 is to be considered as the closest prior art.

2.1.1 Review article D1 teaches that while antibodies to the immunodominant, but highly variable, regions of HA and NA can provide potent virus strain-specific protection, the existence of weaker and more broadly protective immune activities directed to less variable regions of viral proteins had long been known. The most promising approaches for inducing immunity against relatively invariant viral determinants were based on antibodies specific for the relatively conserved ectodomain of matrix protein 2 (M2) (see the abstract; page 571, right-hand column, first full paragraph) and the inter-HA1-HA2 subunit region of haemagglutinin. The degree of sequence diversity between subtypes is described as great, particularly in the HA1 polypeptides (34-59% homology between subtypes); more conserved regions are found in HA2 (51-80% homology between subtypes). The most notable region of conservation is the sequence around the cleavage site, particularly the HA2 N-terminal 11 amino acids, termed fusion peptide, which is conserved among all influenza A subtypes and differs only by two conservative amino acid replacements in influenza B virus. The HA1/HA2 joining region is described as another promising candidate for inclusion in a universal vaccine. Joint-specific immunity in the mouse model has been described as more robust than M2e-specific immunity (see page 572, left-hand column, paragraph 1). Another protective antibody has been shown to bind to a conformational HA2 epitope. It is also noted that HA2-specific antibody responses appear to be induced less effectively than the HA1-specific response by infection in humans (see page 572, left-hand column, first full paragraph).

Review article D1 specifically refers to the data in documents D2 and D3 (see References 32 and 33, page 572, left-hand column, paragraph 1).

Difference, technical effect and objective technical problem to be solved

2.2 The board agrees with the appellant that the difference between the closest prior art and the claimed subject-matter is that the peptide-based vaccine candidates discussed in document D1 are based on conserved and dominant viral determinants of M2 and the HA0 cleavage site of influenza A and B.

Contrary thereto, the claimed subject-matter relates to a relatively large polypeptide lacking at least a portion of or displacing the entire globular head domain (comprising several immunodominant epitopes) in/from the HA1 domain, while maintaining the full HA2 domain (see Figure 10A of the application).

The examples in the application as filed show that vaccination with a "headless" influenza virus HA polypeptide of the claimed invention induces antibodies that are cross-reactive against heterologous influenza virus strains of the same subtype (see paragraph [00409] and Figure 15, for example), whereas vaccination with the full-length influenza virus HA resulted in no cross-reactivity or only a low degree of cross-reactivity to heterologous strains (see, for example, paragraph [00409], Figure 15B, 4th panel; Figure 15C, 4th panel, of the application as filed).

However, no comparative data have been provided to show that the claimed "headless" influenza virus HA polypeptide would result in a better and/or broader

protection against influenza compared to the vaccines disclosed in the closest prior art, i.e. document D1 (see, for example, document D3, Figure 6; page 7386, right-hand column, first full paragraph).

The board is of the opinion that the objective technical problem can be defined as the provision of an alternative HA-based polypeptide suitable as a vaccine.

Obviousness

2.3 The board is not persuaded by the examining division's reasoning that the claimed subject-matter lacks an inventive step in view of the teaching of review article D1 in combination with that of document D4.

The passages in document D1 relating to the HA1/HA2 joining region make reference to documents D2 and D3 (see References 32 and 33).

2.3.1 Document D2 describes a peptide-based vaccination approach (9 to 76 amino acid lengths), showing that the immunogenicity of multipeptide constructs, comprising adjacent sequences of the HA1/HA2 317–341 intersubunit region of immature influenza A HA (H1N1), was dependent on the presence of the hydrophobic fusion peptide, encompassing the N-terminal 1 to 13 sequence of the HA2 subunit (see the abstract and Table 1).

2.3.2 Document D3 discloses that a peptide conjugate subunit vaccine, based on the highly conserved maturational cleavage site of the HA0 precursor of the influenza B virus HA conjugated to a carrier, can elicit an antibody-mediated protective immune response against lethal challenge with viruses belonging to either one of the representative, non-antigenically cross-reactive

influenza B virus lineages. The approach could be extended to influenza A virus, although the equivalent HA0 conjugate is not as efficacious as for influenza B (see the abstract and Table 1).

2.3.3 Document D4 describes directing immune (CD8-T-cell) responses to a subdominant epitope of respiratory syncytial virus (RSV) by way of the "deletion" of an immunodominant epitope of the M2 protein. "Deletion" is performed by mutating [emphasis added]the MHC-II anchor residues of the dominant epitope $M2_{82-90}$ (see abstract; Table 1; page 4776, left-hand column, first full paragraph). Mice were vaccinated with plasmid DNA encoding the unmutated (full-length) and the $M2_{82-90}$ epitope-mutated (full-length) version of the M2-1 protein (see Fig. 2). Mutation of the anchor residues resulted in a redirection of the immune response to subdominant M2 epitopes (see Fig. 3). The mutated vaccine resulted in a significant yet reduced protection relative to the wt M2 molecule (see Table 2).

2.4 What can be derived from documents D1 to D3 is that the HA1/HA2 intersubunit region represents an interesting immunogenic target for eliciting cross-protective responses.

The immunisation strategies disclosed in these documents rely on peptides or multipeptide constructs in which a motive is repeated. However, none of these documents teaches or suggests using the entire HA stem domain and/or HA globular head domain.

2.5 What can be inferred from document D4 is that mutations of MHC-anchoring residues within an immunodominant epitope (i.e. replacements [!] of specific amino acids

by others), confusingly referred to as "deletion" in the title and the discussion of document D4, can redirect the immune response to subdominant epitopes.

2.6 However, none of documents D1 to D4 describes an approach of deleting, i.e. cutting out, at least a portion of, or of displacing, an entire domain (comprising several immunodominant epitopes) in/from the HA1 domain while maintaining the full HA2 domain (see Figure 10A of the application), in order to redirect the immune response to the remaining, immunologically subdominant, part of the molecule.

2.7 Therefore, the board takes the view that the claimed subject-matter is not obvious to a person skilled in the art when considering the teachings in documents D1 to D4 either alone or in combination.

3. Inventive step - Article 56 EPC - in view of documents D9 to D10

3.1 Documents D9 and D10, which were cited in proceedings before other national offices, appear to be highly relevant for the assessment of inventive step.

3.2 Document D9 discloses a truncated H2 subtype-derived HA molecule lacking a significant portion of the globular head domain, which has been shown to offer significant protection to mice upon subsequent challenge with an H1 influenza virus. A conformational epitope located in the middle of the stem region of H1 (comprising residues 318 to 322 of HA1 and 47 to 58 of HA2) and capable of neutralising all H1 and H2 subtypes was not affected by the removal of the globular head part (nucleotides 232 to 873 of H2 deleted). The authors conclude that headless HA has the potential to induce

cross-protection against influenza virus infection. (see, for example, the abstract; the introduction; Fig. 1; page 1 485, left-hand column; Fig. 3).

3.3 Document D10 (apparently the patent counterpart to the scientific article D9) discloses an immunogenic artificial polypeptide antigenically substantially identical to the stem regions of influenza HA but lacking the globular head region (see paragraph [0020], Examples 6 to 9 for the constructs, Examples 10 and 11 for the effects, and claims 8 to 12).

4. It is not evident from the written proceedings whether or not the examining division took documents D9 and D10 into account in its examination of the application.

Given these circumstances, the board, exercising its power under Article 111(1), second sentence, EPC, considers it appropriate to remit the case to the examining division for further prosecution in order to ensure examination of the application with regard to documents D9 and D10.

The appellant has agreed to this approach (see section V. above).

5. As the board has not refused any of the appellant's requests, the present decision can be made without the need for oral proceedings.

Order

For these reasons it is decided that:

- The decision under appeal is set aside.

- The case is remitted to the examining division for further prosecution.

The Registrar: The Chairman:

I. Aperribay W. Sekretaruk

Decision electronically authenticated