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Datasheet for the decision of 12 October 2023

Case Number:	T 1496/21 - 3.3.04
Application Number:	16180926.4
Publication Number:	3109258
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Language of the proceedings:	EN

Title of invention:
Recombinant RSV antigens

Patent Proprietor:
ID Biomedical Corporation of Quebec
GlaxoSmithKline Biologicals s.a.

Opponents:
Janssen Vaccines & Prevention B.V.
Pfizer Inc.

Headword:
RSV antigens/ID BIOMEDICAL CORPORATION

Relevant legal provisions:
EPC Art. 83

Keyword:
Sufficiency of disclosure - (no)

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Beschwerdekammern

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Case Number: T 1496/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 12 October 2023

Appellant: (Patent Proprietor 1)	ID Biomedical Corporation of Quebec 2323 Boul. du Parc Technologique Ste Foy Quebec G1P 4R8 (CA)
Appellant: (Patent Proprietor 2)	GlaxoSmithKline Biologicals s.a. rue de l'Institut 89 1330 Rixensart (BE)
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Respondent I: (Opponent 1)	Janssen Vaccines & Prevention B.V. Archimedesweg 4 2333 CN Leiden (NL)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Respondent II: (Opponent 2)	Pfizer Inc. 235 East 42nd Street New York, NY 10017 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 8 July 2021**

revoking European patent No. 3109258 pursuant to Article 101(3)(b) EPC.

Composition of the Board:

Chairwoman	M. Pregetter
Members:	B. Rutz
	L. Bühler

Summary of Facts and Submissions

I. An appeal was lodged by the patent proprietors (appellants) against the decision of the opposition division to revoke European patent No. 3 109 258. The patent is entitled "*Recombinant RSV antigens*" and is based on divisional European patent application No. 16180926.4. The parent application is European patent application No. 08864495.0, published as international application WO 2009/079796.

II. The patent was opposed on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and of Article 100(b) and (c) EPC.

III. The opposition division decided *inter alia* that the invention to which claim 1 of auxiliary requests 6 to 8 related was not sufficiently disclosed (Article 83 EPC).

IV. With their statement of grounds of appeal, the appellants filed sets of claims of a main request (identical to auxiliary request 6 dealt with in the decision under appeal) and auxiliary requests 1 to 7.

V. Both opponents (respondents I and II) replied to the appeal.

VI. With their letter dated 15 August 2022, the appellants filed auxiliary requests 8 to 11.

VII. The board summoned the parties to oral proceedings as requested and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA.

VIII. With their letter dated 17 July 2023, the appellants filed auxiliary requests 12 and 13.

IX. With its letter dated 4 October 2023, respondent I withdrew its request for oral proceedings and stated that it would not be represented at the oral proceedings.

X. Claim 1 of the main request reads as follows:
"1. A recombinant respiratory syncytial virus (RSV) antigen which assembles into a trimer, comprising a soluble F protein polypeptide comprising an F_2 domain and an F_1 domain of an RSV F protein polypeptide and comprising an amino acid sequence comprising a heterologous trimerization domain positioned C-terminal to the F_1 domain that stabilizes the prefusion conformation of the F protein."

Claim 5 of the main request reads as follows:
"5. An immunogenic composition comprising the recombinant RSV antigen of any one of claims 1-3, and a pharmaceutically acceptable carrier or excipient."

Claim 7 of the main request reads as follows:
"7. The use of the RSV antigen of any one of claims 1-3 or the recombinant nucleic acid of claim 4 in the preparation of a medicament for treating an RSV infection."

Claim 8 of the main request reads as follows:
"8. The recombinant RSV antigen of any one of claims 1-3 or the immunogenic composition of any one of claims 5-6 for use in the prevention or treatment of RSV-associated diseases."

XI. Oral proceedings before the board took place on 12 October 2023 in the absence of respondent I, as announced in the letter dated 4 October 2023. During the oral proceedings, the appellants withdrew all auxiliary requests. At the end of the oral proceedings, the Chairwoman announced the board's decision.

XII. The following documents are cited in the present decision:

D6 WO 2008/154456

D16 A. Rigter et al., "*A Protective and Safe Intranasal RSV Vaccine Based on a Recombinant Prefusion-Like Form of the F Protein Bound to Bacterium-Like Particles*", PLOS ONE 8(8), 2013, 1-14.

D18 J. S. McLellan et al., "*Structure of RSV Fusion Glycoprotein Trimer Bound to a Prefusion-Specific Neutralizing Antibody*", Science 340(6136), 2013, 1113-1117 incl. Supplementary Materials, 1-18.

D19 N. Blais et al., "*Characterization of Pre-F-GCN4t, a Modified Human Respiratory Syncytial Virus Fusion Protein Stabilized in a Noncleaved Prefusion Conformation*", Journal of Virology 91(13), 2017, 1-18.

D21 I. Widjaja et al., "*Recombinant Soluble Respiratory Syncytial Virus F Protein That Lacks Heptad Repeat B, Contains a GCN4 Trimerization Motif and Is Not Cleaved Displays Prefusion-Like Characteristics*", PLOS ONE 10(6), 2015, 1-19.

D29 J. S. McLellan et al., "*Structure-Based Design of a Fusion Glycoprotein Vaccine for Respiratory Syncytial Virus*", Science 342(6158), 2013, 592-598 incl. Supplementary Materials 1-30.

D57 Experimental evidence submitted by opponent 1, 2021, 4 pages

D58 WO 2018/176103

XIII. The appellants' arguments, where relevant to the decision, may be summarised as follows.

Claim interpretation

The term "stabilizes" in claim 1 should be given a broad definition in the light of the description and should be considered met if:
(1) there was an improvement in stability of the prefusion conformation relative to the absence of the trimerisation domain, and
(2) a substantial portion of the expressed protein was detected in the prefusion conformation.

The "stabilizes" feature required an improvement in stability of the prefusion form conferred by inclusion of the trimerisation domain, which could be observed through detecting a substantial portion of the prefusion form when expressed. This was the broadest technically sensible interpretation of the feature (see e.g. T 79/96, reasons 2.1.3; T 596/96, reasons 3.2).

The antigen of claim 1 was a preF antigen which was detectable by specific antibodies and capable of eliciting a specific immune response.

Sufficiency of disclosure (Article 83 EPC)

The patent provided a clear disclosure of the stabilising effect of a heterologous trimerisation domain on the prefusion form of RSV F, exemplifying expression of such an antigen and its ability to generate a protective immune response. The claims did not require any particular duration/extent of stability under particular conditions. Evidence alleged to illustrate insufficient disclosure related to arbitrary conditions of storage stability, which did not reflect any teaching in the patent or any practical requirement for carrying out the invention. This evidence thus did not provide any verifiable facts of insufficiency, much less serious doubts.

The patent disclosed and claimed, as a minimum, the level of stabilisation inherent in a construct with a C-terminal trimerisation domain. This measure of stabilisation was suitable for inducing an immune response and protection against disease. There was no difference between the stabilisation requirements of the different claim categories (antigen, immunogenic composition and medical use).

The evidence relied on by the respondents demonstrated that constructs falling within the scope of the claims were "more stable" through the addition of only a trimerisation domain (see, e.g. D16, D18 and D29).

The data in document D6 related to a construct which fell within the allowed failures that could

occasionally occur. Moreover, the resolution of the error was clearly within the normal workings of a skilled person, especially given that D6 suggested that the error was introduced by the inclusion of additional unnecessary residues in the construct.

Document D19 explicitly stated that the trimerisation domain used contributed to the stabilisation of the prefusion conformation.

Document D57 also showed that a construct in accordance with the invention was stable in the prefusion state upon expression. The fact that the stability may drop after that was not relevant.

Document D58 provided an example of a chimeric polypeptide comprising only the RSV F ectodomain and a "clamp" trimerisation domain which was stabilised in a trimeric prefusion state.

The evidence on file thus indicated that the addition of only a trimerisation domain to a soluble RSV F antigen construct could functionally stabilise the prefusion trimer such that a substantial portion of the antigen was detectable in the prefusion form upon expression.

XIV. The respondents' arguments, where relevant to the decision, may be summarised as follows.

Claim interpretation

In view of the teaching of the patent the compositions of the alleged invention were for use as a medicament and in particular for eliciting an immune response (see paragraphs [0001], [0005] and [0014] of the patent).

The prefusion conformation was required to be stabilised and maintained so that it could be manufactured in a viable manner.

"Stabilize" required that the immunological character of the prefusion conformation was maintained meaning that the expressed protein should not only be detectable in the prefusion conformation at some point of the production process, but should also be maintained in that conformation following administration into a cellular or extracellular environment to allow an immune response and/or a therapeutic treatment (see paragraphs [0014] and [0063]).

Sufficiency of disclosure (Article 83 EPC)

The patent itself taught that the prefusion state would be unstable without further modifications. Paragraphs [0065] to [0068] of the patent discussed several further stabilising modifications, including the deletion or removal of one or both of the furin cleavage sites. Paragraph [0067] noted that deleting one or both furin cleavage sites prevented the fusion peptide from being cleaved from the F2 domain and released from the globular head, and explained the importance of this modification to avoid instability of the prefusion conformation. The teaching that F proteins that retain their furin cleavage sites would release the fusion peptide from the globular head of the prefusion conformer in the presence of cell membranes (i.e. in the cellular or extracellular environment) meant that they would be susceptible to transition to the post-fusion state.

Document D6 could not be considered to represent an "occasional failure" in the absence of any other evidence demonstrating a working embodiment wherein a trimerisation domain alone provided a stable, prefusion conformation F protein suitable for eliciting an immune response in a subject. In fact, it was clear from e.g. documents D29 and D16 that the addition of a trimerisation domain alone did not satisfy the requirements of claim 1 and therefore the skilled person could not obtain substantially all the embodiments falling within the claims.

The evidence on file showed that a trimerisation domain by itself was insufficient to stabilise the RSV F protein in a prefusion conformation. The documents submitted constituted verifiable facts that the invention to which claim 1 related was not sufficiently disclosed.

XV. The appellants (patent proprietors) requested that the decision under appeal be set aside and that the case be remitted to the opposition division for further prosecution, alternatively, that the patent be maintained in amended form on the basis of the claims of the main request filed with the statement of grounds of appeal.

Respondent II (opponent 2) requested that the appeal be dismissed and the decision to revoke the patent be upheld, alternatively, that the case be remitted to the opposition division for further prosecution.

Respondent I (opponent 1) had requested in writing that the appeal be dismissed and the decision to revoke the patent be upheld.

Respondent I further requested that none of the claim requests should be admitted into the appeal proceedings.

Reasons for the Decision

Right to be heard (Article 113 EPC)

1. Respondent I who was not represented at the oral proceedings as announced was treated as relying on its written case according to Article 15(3) RPBA.

Technical background

2. The patent relates to the development of vaccines to prevent respiratory syncytial virus (RSV) infection. Since inactivated RSV virus as a vaccine has proven ineffective and has even resulted in more severe disease, alternative forms of vaccines are sought. As for other enveloped viruses, preferred antigens in a recombinant vaccine are the proteins on the outside of the virus, in the case of RSV the Fusion (F) protein. To be suitable as an antigen in a vaccine, this membrane protein needs to be brought into a soluble form by replacing the membrane domain. The F protein exists in a meta-stable prefusion form which upon contact with host cells, but also in the absence of the membrane domain, rapidly converts into a more stable postfusion conformation by a large scale structural rearrangement (see e.g. figure 1 in document D21, reproduced below).

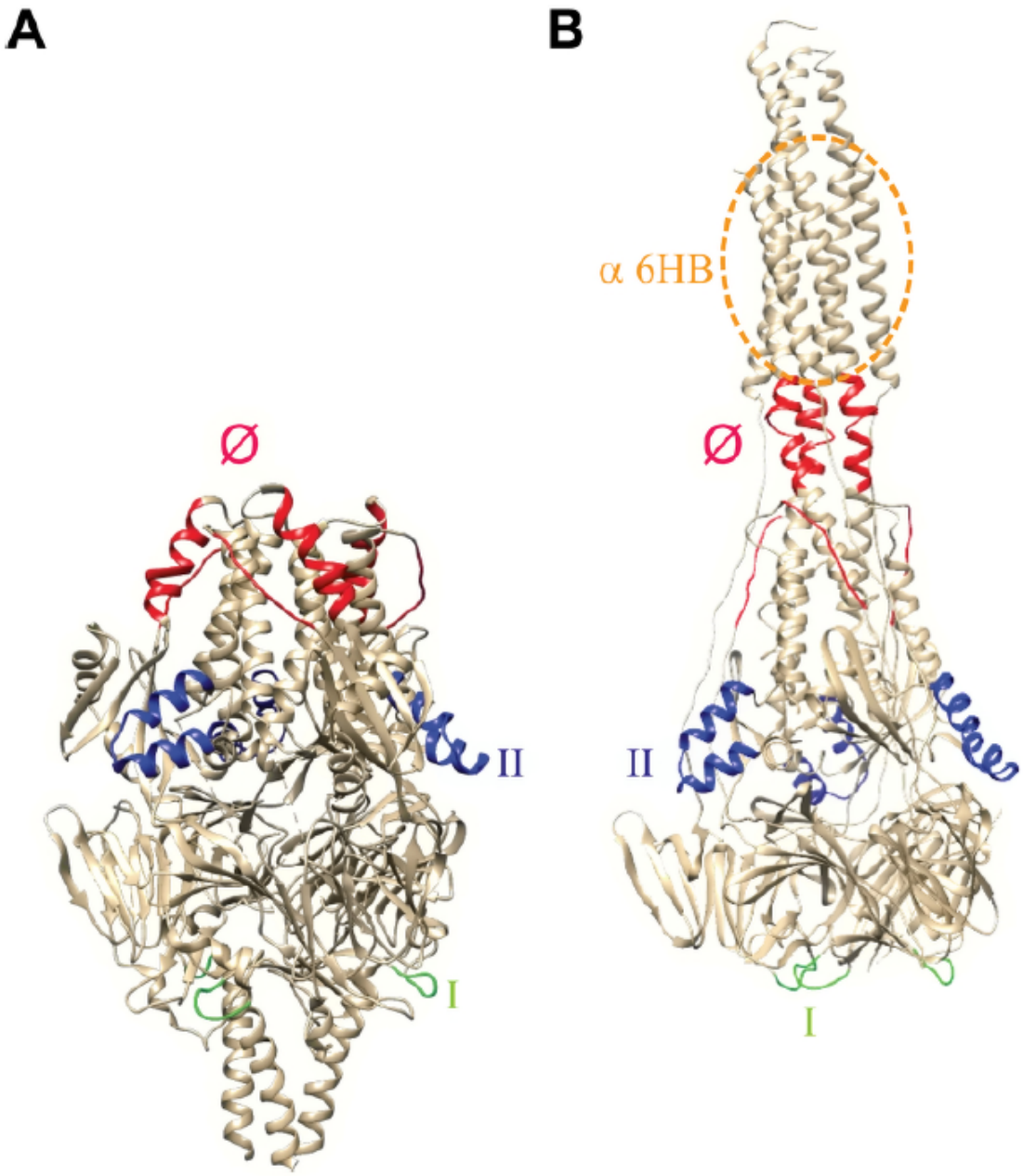


Fig 1. Overview of antigenic sites on pre- and postfusion F. (A) prefusion [8] and (B) postfusion [10] structures of RSV F. Antigenic sites recognized by antibodies used in this study are indicated (according to [8]): site I (green; recognized by MAb 131-2a), site II (blue; recognized by MAb Palivizumab), and site Ø (red; recognized by MAbs D25 and AM22). The region to which the α6HB PAb binds is indicated by the dotted orange circle. Site Ø is disrupted in postfusion F, while site I appears to be shielded in the prefusion conformation.

3. This structural rearrangement leads to the loss of the most relevant neutralising epitopes (e.g. the Ø epitope) and thus renders the postfusion conformation unsuitable for use in a vaccine. The patent aims to

provide F protein analogs called "PreF" or "PreF antigen" which stabilise the prefusion conformation in order to allow the immune system to react with the relevant epitopes. This is based on the prediction that an immune response generated to the prefusion conformation of F would preferentially include antibodies that would prevent binding, conformation shifting and/or other events involved in membrane fusion upon viral infection, thereby increasing the efficacy of the protective response. In the examples of the patent, the PreF antigen contains an added C-terminal trimerisation domain ("Coiled-coil") and lacks the proteolytic cleavage sites ("Fur 1" and "Fur 2") and the intervening peptide ("pep 27", see examples and part of fig. 1 of the patent, reproduced below).

FIG. 1A

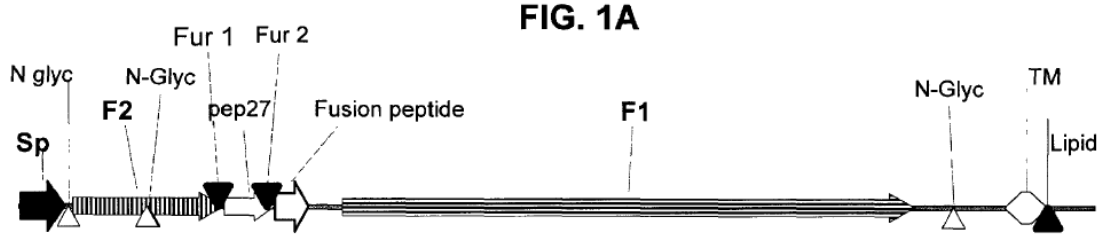
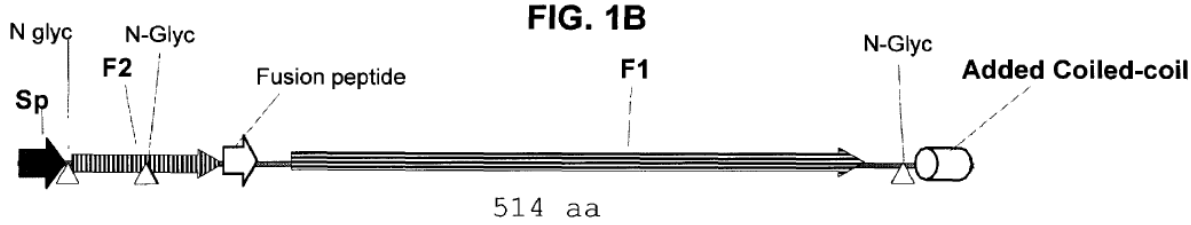


FIG. 1B



Main request
Admittance (Article 12(2) RPBA)

4. Respondent I requested that none of the claim requests be admitted into the proceedings. The main request was filed as auxiliary request 6 during opposition proceedings. This request was considered in the

decision under appeal. It therefore forms part of the appeal proceedings according to Article 12(2) RPBA.

Claim interpretation

5. Claim 1 requires that the recombinant respiratory syncytial virus antigen "*assembles into a trimer*" and comprises "*a heterologous trimerization domain positioned C-terminal to the F_1 domain that stabilizes the prefusion conformation of the F protein*". The features "*assembles into a trimer*" and "*stabilizes the prefusion conformation*" thus relate to inherent properties of the claimed antigen. All further independent claims, in particular claim 5 defining an immunogenic composition and claims 7 and 8 relating to further medical uses, refer to the antigen of claim 1 and thus also contain the antigen having these properties.

6. The term "*stabilizes the prefusion conformation*" in the absence of other comparative instances in the claim means that the antigen comprising the trimerisation domain has to be more stable in the prefusion conformation than an RSV F protein antigen lacking said domain. Claim 1, however, does not define a time period or particular conditions under which the prefusion conformation has to be more stable. From the term "stabilizes" on its own, and adopting a literal interpretation, any degree of stabilisation even to a minor extent and for a very short period of time or under specific conditions could thus be considered to suffice.

7. The board, however, recalls that claim 1 defines an antigen, more particularly an RSV antigen having a certain conformation. The skilled person will consider

this context when interpreting the term "stabilizes" in a technically meaningful way.

8. In view of the technical field of the patent and its purpose to provide "*compositions and methods for eliciting an immune response specific for Respiratory Syncytial Virus (RSV)*" (see paragraph [0001]), stabilising the prefusion conformation is understood by the skilled person to mean that the claimed antigen retains at least one immunodominant epitope of the prefusion conformation of the F protein (see paragraph [0014]) and that this epitope is also maintained following introduction of the PreF antigen into a cellular or extracellular environment (see paragraph [0063]). The appellants' argument during the oral proceedings to the effect that expression of the protein in a bacterial or other cellular system also had to be considered as "*introduction of the PreF antigen into a cellular or extracellular environment*" is not found persuasive because, from the context of paragraph [0063] and the reference to "*immunogenic epitopes*" therein, the skilled person would consider "introduction" to relate to a subject capable of an immune response and not to cells in culture. This is supported by the reference to "*for example, in vivo e.g. following administration to a subject*" in the same sentence.

9. The function of the C-terminal trimerisation domain in stabilising the prefusion conformation is therefore linked to the immunogenic function of the claimed antigen. This was confirmed during oral proceedings by the appellants who agreed that the antigen of claim 1 had to be capable of inducing a specific immune response to the prefusion conformation of the F protein. The appellants further agreed that the term

"stabilizes" had to be interpreted in the same manner in claims 1, 5, 7 and 8, i.e. independently of whether the claim related to an antigen, an immunogenic composition or a further medical use in the Swiss-type format or in the format prescribed by Article 54(5) EPC.

10. The board concludes that a certain extent of stabilisation which goes beyond mere detectability after expression is required so as to allow the chimeric F protein to function as a prefusion conformation antigen which can elicit a specific immune response.

Sufficiency of disclosure (Article 83 EPC)

11. The patent contains experimental evidence for the combination of three modifications of the F protein to obtain stabilisation of the prefusion conformation (see figure 1 and paragraph [0152]):
(i) addition of a coiled-coil domain at the C-terminal end of the extracellular domain of the F0 polypeptide replacing the membrane anchoring domain of F0;
(ii) removal of the pep27 sequence between the F2 and F1 domains;
(iii) elimination of both furin motifs (Fur1 and Fur2).

12. The patent does not contain data which show that "*a heterologous trimerization domain* [of any kind] *positioned C-terminal to the F_1 domain*" in the absence of other modifications (see point 11. above) achieves stabilisation of the prefusion conformation.

13. In view of the claim interpretation above (see points 5. to 10.), the question arises as to whether the invention to which the claim relates, i.e. the

provision of an antigen capable of inducing a specific immune response against the prefusion conformation of the RSV F protein, could be carried out by the skilled person over the whole scope of the claim.

14. The respondents provided evidence to substantiate their doubts that the addition of a C-terminal trimerisation domain in the absence of other modifications was sufficient for achieving a specific immune response against the prefusion conformation of the F protein.

15. Document D29 states on page 592, right-hand column, "[t]*o stably present antigenic site Ø in the absence of* [the antibody] *D25, we retained the C-terminal trimerization domain and combined it with other means of stabilization, including the introduction of cysteine pairs or cavity-filling hydrophobic substitutions*". Table S1 in the Supplementary materials of D29 shows that the prefusion conformation of a construct containing only the trimerisation domain ("*RSV F wild type with C-terminal foldon*") is detectable with antibody D25 in an ELISA binding assay 5 days after transfection (see figure S4 in the Supplementary Materials), but detection is strongly reduced after further storage for one week at 4 °C (see table S1 in the Supplementary Materials).

16. The appellants argue that "*D29 thus provides clear evidence that when a wild type RSV F is solely modified with a C-terminal foldon (trimerization) domain, good binding to prefusion-specific antibody D25 is seen post-expression. Hence, the prefusion conformation of RSV-F has been stabilized*". The board agrees that detection of the prefusion form post-expression has been achieved in D29. However, the authors of D29 introduced further modifications "[t]*o stably present*

antigenic site Ø in the absence of D25" indicating that the addition of the trimerisation domain alone was not considered sufficient when the stabilising antibody was absent. D29 thus provides evidence for detection of the prefusion conformation after expression in cell culture supernatant (see figure S4) but not for the stabilisation required for purification, administration and obtaining a specific immune response.

17. Document D57 shows the results of a 4-day period of storage of expressed F protein constructs with or without a C-terminal foldon domain. After two days, no or very small amounts of F protein in the prefusion state remain detectable with three different prefusion specific antibodies (see D57, figure 1). Similar to the results in D29, the appellants considered these results as proof that on day zero, i.e. the day of harvest of the cell culture, the F protein with the foldon domain showed a higher proportion of prefusion conformation than the F protein without it. Similarly to D29, D57 shows the prefusion conformation after expression, but does not show that trimerisation alone was sufficient to maintain the prefusion conformation during purification and administration into a subject.

18. Document D16 states in its abstract that "*the recombinant soluble ectodomain of RSV F readily adopts a postfusion conformation, generation of which cannot be prevented by C-terminal addition of a trimerization motif, but whose formation is prevented by mutation of the two furin cleavage sites in F*". On page 9, right-hand column, last paragraph, it concludes that "*addition of an artificial trimerization motif to the carboxy terminus of the soluble cleaved F protein (Fwt-GCN) did not prevent the F protein from adopting the postfusion conformation, as judged by the formation of*

the SDS-resistant, heat-sensitive, higher-order structure". The observation by the appellants that the Fwt-GCN construct (wild-type RSV F with a GCN4 trimerisation domain) bound slightly better to prefusion specific antibodies than Fwt (wild-type RSV F, see figure 4) is not in dispute. In contrast to the experiments in D29 and D57, in D16 the prefusion form is detected with purified protein (see legend to figure 4), thus indicating that the prefusion conformation of Fwt-GCN is at least partially maintained during purification. However, the question remains as to whether the detected minor improvement in binding is sufficient evidence for stabilisation of the prefusion conformation so as to elicit a specific immune response, when the authors of D16 report that the Fwt-GCN construct "*readily adopts a postfusion conformation*" and forms "[an] *SDS-resistant, heat-sensitive, higher-order structure*" which the skilled person would consider incompatible with achieving a specific immune response to the prefusion conformation.

19. Document D18 states on page 1115, left-hand column, that "[t]*he addition of the fibritin domain was not, however, sufficient to stabilize RSV F in the prefusion state, suggesting that it is not an optimal substitute for the native transmembrane domains that normally stabilize F in the viral membrane (34). The binding of antibody D25 was thus required to stabilize the prefusion trimer*". The stabilising antibody D25 was either co-expressed or added as a purified antibody three hours post-transfection to the cells (see Supplementary Materials paragraph bridging pages 3 and 4 and figure S1). D18 in this regard also states on page 1114, middle column that the authors "*failed to form complexes by mixing purified RSV F(+) Fd with purified D25 or AM22, suggesting that F was triggered*

during purification (25). To capture F in its prefusion state, RSV F(+) Fd was expressed as a complex with D25". The board does not agree with the appellants' argument that the complexes mentioned in this passage in D18 were specific for crystallisation and required particular characteristics, such as high homogeneity. As apparent from the Supplementary Materials, page 4, first paragraph, the complex between F protein and antibody is formed by addition of the antibody to the supernatant without any further purification. The question, therefore, remains as to whether the necessary addition of an antibody to the supernatant three hours after transfection for stabilisation of the prefusion form is compatible with the antigen being capable of inducing a specific immune response against the prefusion form.

20. D18 furthermore reports on page 1115, left-hand column, that "*RSV F could not be expressed with the GCN4 motif, but could be expressed with the fibritin trimerization domain (24)*". GCN4 is one of the trimerisation domains disclosed in the patent as "*one favorable example of a trimerization domain*" (see paragraph [0064] and SEQ ID NO: 11). Similar to the disclosure in D6 (see points 22. and 23. below), this raises serious doubts as to whether the skilled person was able to achieve the claimed antigen with each and every trimerisation domain.

21. Document D19 states on page 11, first paragraph: "*More particularly, the two furin sites and pep27 were deleted. As a result, the FP remains attached to the C terminus of F2, preventing a structural translocation of approximately 100 Å that would normally be required for the formation of the post-F 6HB. In line with results obtained by others, the removal of pep27*

allowed the folding of the protein in its trimeric form (42, 44, 54)". The appellants considered the disclosure of D19 to be evidence that the trimerisation domain contributed to the stabilisation of the prefusion conformation. While this appears indeed the case the results reported in D19 do not support the conclusion that the trimerisation domain alone provides the necessary stabilisation to obtain a specific immune response.

22. Document D6 reports a coiled-coil trimerisation domain which upon addition to the F protein distorts the structure and does not lead to a prefusion form: "*The sF protein with the GCNt clamp that we produced, sMP340-A, is secreted efficiently from transfected cells but it is not recognized efficiently by MAbs against the F protein, may be partially aggregated, and is not triggered by treatment at 50 °C for one hour*" (see paragraph [0086]). This is interpreted by the authors as "*suggesting that this protein is not in the pre-triggered form to begin with and could not be triggered (Fig. 15). It is possible that the GCNt trimerization domain distorts the RSV sF protein. However, it is also possible that the GCNt domain that we added to the sF sequence was not in the proper phase with the HR2 domain, resulting in a distorted protein*" (see paragraph [00204]).

23. The data in D6 thus shows that a construct with a trimerisation domain was not stabilised in the "*pre-triggered form*" and aggregated (see paragraphs [00203] and [00204]). A construct falling under the structural definition of claim 1 thus does not achieve the functional requirement to "stabilize" the prefusion conformation. The appellants consider this to "*fall within the allowed failures that can occasionally*

occur" and which the skilled person would be able to correct based on the explanations provided in D6. The board does not agree because D6 only provides a speculative explanation as to why the disclosed construct did not work without providing a clear instruction on how to modify the GCNt domain. More importantly, the patent is silent on how to adapt a trimerisation domain in order to achieve "*the proper phase with the HR2 domain*" nor can this be considered common general knowledge. The disclosure of the sMP340-A construct in D6 and the GCN4 domain in D18 (see point 20. above) thus provide examples falling under the structural definition of claim 1 which do not achieve an antigen capable of inducing a specific immune response.

24. In summary, the respondents have provided evidence that substantiates serious doubts that the prefusion conformation of the RSV F protein can be sufficiently stabilised by a trimerisation domain alone to achieve a specific immune response against the prefusion conformation (see documents D16, D18, D29, D57, discussed above). The respondents have further provided examples of recombinant proteins falling under the structural definition of claim 1 which cannot be expressed, have a distorted structure or aggregate and are thus not functional as antigens (see documents D6 and D18, discussed above).

25. The appellants have provided no evidence which can be seen to dispel the serious doubts raised by the respondents. In particular the appellants have not provided evidence that, in the absence of further modifications, a trimerisation domain could stabilise the prefusion conformation sufficiently to achieve a specific immune response against that conformation.

26. Post-published document D58 provided by the appellants is not considered sufficient because it involves a specific construct, the "SSM clamp", which was not known to the skilled person at the time of filing. Although this construct is based on a coiled-coil motif which is also mentioned in the patent, the specific sequence and characteristics of the SSM clamp were not known. The example of a specific trimerisation domain capable of stabilising the prefusion conformation is not considered sufficient to show that trimerisation domains of any sort are capable of stabilising the prefusion conformation in a way to allow a specific immune response. Moreover, although the RSV F protein containing the SSM clamp trimerisation domain could be detected in the prefusion conformation in purified form (see D58, figure 1A), the immunisation experiments were carried out with a different form of the RSV F ectodomain in which the furin cleavage motifs and the pep27 sequence had been deleted (see example 6).

27. The board concludes that the prior art suggests that additional modifications are necessary for a stabilised prefusion conformation capable of inducing a specific immune response, in particular the mutation or deletion of the furin cleavage sites and the deletion of the p27 linker.

28. The board thus finds that the patent does not provide sufficient information on how to obtain an RSV antigen in which the prefusion conformation of the F protein is stabilised by (merely) adding a heterologous trimerisation domain to the C-terminus of the F1 domain.

29. The invention to which claim 1 relates is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated