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Language of the proceedings: EN

Title of invention:
Targeted gene delivery for dendritic cell vaccination

Applicant:
California Institute of Technology

Headword:
Targeted gene delivery dendritic cell vaccination/CALIFORNIA INSTITUTE TECHNOLOGY

Relevant legal provisions:
EPC Art. 83, 84
RPBA 2020 Art. 17

Keyword:
Main and sole request - clarity (no); supported by the description (no);

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 1245/17 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 10 September 2021

Appellant: (Applicant)	California Institute of Technology 1200 East California Boulevard, M/S 201-85 Pasadena, CA 91125 (US)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 30 November 2016 refusing European patent application No. 12158285.2 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	P. Julià
	R. Winkelhofer

Summary of Facts and Submissions

I. European patent application no. 12 158 285.2 (published as EP 2 526 774; hereinafter "the patent application"), is a divisional application of the European patent application no. 07 799 765.8 (published as EP 2 048 955) originally filed under the PCT and published as WO 2008/011636. The patent application was refused by an examining division of the EPO for lack of clarity and insufficiency of disclosure (Articles 84 and 83 EPC). Basis for the refusal was a main and sole request filed on 30 August 2016.

II. The applicant (appellant) lodged an appeal and requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request underlying the decision under appeal. As an auxiliary measure, oral proceedings were requested.

III. The board summoned the appellant to oral proceedings scheduled for 18 January 2022. In a communication pursuant to Article 17 of the Rules of Procedure of the Boards of Appeal (RPBA 2020), the appellant was informed of the board's provisional opinion on the issues of the case.

IV. On 15 July 2021, the appellant, without making any substantive submissions, informed the board of their intention not to be represented at the oral proceedings.

V. The board cancelled the oral proceedings and informed the appellant that it intended to issue a decision in line with the provisional opinion as summarised in the

conclusions set out in the communication pursuant to Article 17 RPBA 2020.

VI. The set of claims 1 to 7 of the main and sole request underlying the decision under appeal was directed to a recombinant retrovirus. Claim 1, the sole independent claim, reads as follows:

"1. A recombinant retrovirus comprising a retroviral vector encoding a gene of interest and which is pseudotyped with a modified E2 alphavirus glycoprotein, for use in a method of treatment of a mammal;
wherein;
said gene of interest is an antigen;
said modified E2 alphavirus glycoprotein specifically targets DC-SIGN; and
said treatment stimulates an antigen-specific T-cell response to said antigen."

VII. The objection raised by the examining division under Articles 83 and 84 EPC concerned the feature "specifically targets DC-SIGN" in claim 1.

According to the examining division, in the absence of a clear indication in the claim of how to achieve this effect, this feature only represented a reference to a desirable characteristic or property (Article 84 EPC). The patent application neither supported nor disclosed any such glycoprotein having this property or effect and there was no common general knowledge of this kind available to the person skilled in the art (Articles 84 and 83 EPC). The patent application neither supported nor disclosed "a modified E2 alphavirus glycoprotein or a modified Sindbis virus E2 glycoprotein specifically targeting DC-SIGN" (claims 1 and 6, respectively). The examining division further concluded that the claims

lacked clarity, because of the attempt to define the glycoprotein by reference to a result to be achieved (Article 84 EPC).

VIII. The arguments of the appellant, insofar as relevant to the present decision, may be summarised as follows:

Claim 1 was directed to a recombinant retrovirus comprising a retroviral vector with a modified E2 alphavirus glycoprotein that specifically targeted DC-SIGN; the DC-SIGN targeting/specificity was provided by the modified glycoprotein itself, rather than *via* an antibody linkage. Claim 1 included all the essential features necessary for solving the technical problem with which the patent application was concerned, namely the provision of a further virus for use in a method of treatment specifically binding to dendritic cells. A skilled person would have understood, using normal knowledge and skills, the meaning of the functional feature that the "modified E2 alphavirus glycoprotein specifically targets DC-SIGN". This functional feature captured the contribution of the patent application to the art and could not be defined more precisely without restricting the scope of the invention. Moreover, the instructions provided by this feature were sufficiently clear for the skilled person to reduce them to practice without undue burden.

The patent application not only exemplified one particular way of modifying the E2 glycoprotein, i.e. by providing mutations of the heparan sulfate (HS) binding site of E2, but also taught the skilled person how equivalent mutations could be obtained. The examples in the patent application described the engineering, production and use of a SVGmu Sindbis alphavirus to transduce dendritic cells and to raise an

immune response *in vitro* and *in vivo*. As illustrated in Figure 1, the SVGmu glycoprotein included a mutation at the HS binding site to abolish its binding ability; as such, SVGmu was capable of binding DC-SIGN but not heparan sulfate. However, the patent application taught far more than just this embodiment. The description of the patent application, such as for instance in paragraph [0061], taught also other, standard, modifications that could be made to the glycoprotein using standard methods known in the art in order to achieve the same effect. The skilled person was aware of these standard methods at the relevant date as shown, for instance, by document (1) (WO 00/61772), which disclosed various changes to alphavirus glycoproteins that could be made to target dendritic cells (DCs). More generally, methods such as protein engineering and DNA shuffling were also known in the art; the application of oligonucleotide mutagenesis was not new as such and it was a routine technique that could have been performed by the skilled person without undue burden. The skilled person would have been able to apply this or other similar means to obtain further alpha virus glycoproteins that achieved the same technical effect as that demonstrated with SVGmu.

IX. The appellant (applicant) requests that the decision under appeal be set aside and that a patent be granted on the basis of the main and sole request underlying the decision under appeal, filed on 30 August 2016.

Reasons for the Decision

1. The present decision is based on the same grounds, arguments and evidence on which the board's provisional opinion was based. It was neither questioned by the appellant, nor did other aspects come up that would require its consideration.

2. In the decision under appeal, the examining division refused the patent application solely on the basis of Articles 84 and 83 EPC; no other objections were raised against the main and sole request.

The disclosure of the patent application

3. Example 1 of the patent application identifies the Sindbis virus (SV) as a member of the *Alphavirus* genus and discloses the engineering of a dendritic cell (DC) specific targeting molecule based on the Sindbis virus envelope glycoprotein (SVG). It is stated that, taking advantage of the physical separation of the two receptor-binding sites on the SVG, the receptor was engineered to be blind to its canonical binding target heparin sulfate (HS) and to leave intact its ability to interact with the dendritic cell C-type lectin-like surface receptor DC-SIGN (Dendritic Cell Specific ICAM-3 (Intracellular Adhesion Molecules 3)-Grabbing Non-integrin, also known as CD209; paragraph [0056]). In this context, reference is made to Figure 1, wherein both the HS and the DC-SIGN recognition sites are shown to be physically separated within the Sindbis virus E2 glycoprotein (cf. paragraph [0223]).

4. Paragraph [0224] describes the generation of plasmid pSVG (obtained by cloning the cDNA for the wild-type SVG into the commercial pcDNA3 vector) and the specific

mutations performed to disrupt the HS-binding site and to decrease the HS-specific infection. In particular, a ten residues tag sequence was inserted into the E2 glycoprotein between amino acids 71 and 74, and residues 157KE158 were mutated to 157AA158 (cf. paragraph [0224]). Residues 61 to 64 of the E3 glycoprotein were also deleted. The mutated SVG was designated SVGmu (SEQ ID NO: 11) and the cDNA for SVGmu was cloned downstream of the CMV promoter in the pcDNA3 vector resulting in the pSVGmu vector (SEQ ID NO: 3) (cf. paragraph [0225]).

5. Example 2 describes the preparation of recombinant SVGmu-pseudotyped lentiviruses (FUGW/SVGmu) with DC-specificity obtained by transfecting 293T cells with the lentiviral vector FUGW (SEQ ID NO: 1), the envelope plasmid SVGmu and the packaging plasmids (pMDLg/pRRE and pRSV-Rev) (cf. paragraphs [0226]-[0228]).

6. Examples 3 to 9 describe several *in vitro* and *in vivo* studies with recombinant SVGmu-pseudotyped lentiviruses (FUGW/SVGmu) showing the DC-specificity and DC-effects (DC-activation) of these recombinant lentiviruses (cf. paragraphs [0229]-[0250]). Example 10 discloses the construction of a recombinant lentivirus vector (FOVA; SEQ ID NO: 2; Figure 8 top) expressing the chicken ovalbumin (OVA) and the preparation of a recombinant SVGmu-pseudotyped lentivirus expressing OVA (FOVA/SVGmu). This recombinant lentivirus effectively delivered antigens to DCs and stimulated $CD8^+$ and $CD4^+$ T-cell responses (cf. paragraphs [0251]-[0255]).

7. Examples 11 to 14 were summarised by the appellant in the statement of grounds of appeal. As stated by the appellant, these examples showed that the exemplified recombinant lentivirus FOVA/SVGmu targeted the OVA

antigen into the DCs *in vivo*, efficiently stimulated antigen-specific T cells, and induced a strong immune response (cf. Example 11, paragraphs [0256]-[0259]). The results showed an induction of both cellular and humoral immune response against the OVA antigen (cf. Example 12, paragraphs [0260]-[0265]). Using tumor cell lines in which OVA served as the tumor antigen, Examples 13 and 14 showed the effective preventive protection and tumor treatment by the recombinant lentivirus FOVA/SVGmu (cf. paragraphs [0266]-[0270]).

8. Further examples of the patent application concern, *inter alia*, the *in vivo* delivery of DC maturation factors (by adapting the recombinant lentivirus vectors to co-express the OVA antigen and a DC maturation factor) and the preparation of a HIV/AIDS antigen vaccination (cf. Examples 15 to 24, paragraphs [0271]-[00297]).

9. Under the general heading "Detailed description of the preferred embodiment", the patent application describes the targeting molecules (cf. paragraphs [0099]-[0120]), vectors (cf. paragraphs [0121]-[0141]), viral vector and packaging cells (cf. paragraphs [0142]-[0177]), and the delivery of recombinant virus (cf. paragraphs [0178]-[0187]). Paragraphs [0006]-[0022] and paragraphs [0055]-[0064] provide a description of these embodiments in more general terms, the former paragraphs under the heading "Summary of the invention".

The claimed subject-matter

10. Claim 1 is directed to a recombinant retrovirus comprising a retroviral vector encoding a gene of interest and which is pseudotyped with a modified E2

alphavirus glycoprotein, for use in a method of treatment of a mammal; wherein said gene of interest is an antigen, said modified E2 alphavirus glycoprotein specifically targets DC-SIGN, and said treatment stimulates an antigen-specific T-cell response to said antigen.

11. There is no limitation in claim 1 as regards the genus and species of the claimed recombinant retrovirus and of the retroviral vector comprised in said recombinant retrovirus. Only claim 4 requires the retroviral vector encoding a gene of interest to be a lentiviral vector, which is further defined in claim 5 by requiring said lentiviral vector to comprise sequences from a Murine Leukemia Virus (MLV) genome or an HIV genome.

12. Claim 1 requires the recombinant retrovirus to be pseudotyped with a modified E2 alphavirus glycoprotein. According to the patent application, a pseudotyped retrovirus is "a retroviral particle having an envelope protein that is from a virus other than the virus from which the RNA genome is derived" (cf. paragraph [0091]). This definition does not exclude from the scope of claim 1 recombinant retroviruses from the genus alphavirus. Claim 1 comprises recombinant alphaviruses, such as those cited in paragraph [0091], namely Sindbis virus, Semliki Forest virus, Ross River virus and Aura virus, but requires - by using the term "pseudotyped" - that the "modified E2 alphavirus glycoprotein" is derived from an alphavirus species different from that of the claimed recombinant alphavirus. In other words, a recombinant Sindbis virus comprising a retroviral vector encoding a gene of interest and which is pseudotyped with a modified E2 glycoprotein from any alphavirus other than Sindbis virus - and having all other features defined in

claim 1 - falls within the scope of claim 1. The claimed recombinant retroviruses are not limited to those exemplified in the patent application, namely recombinant lentiviruses comprising a lentiviral vector encoding a gene of interest and which are pseudotyped with a modified E2 glycoprotein from Sindbis virus, i.e. the subject-matter of dependent claims 4 to 6.

13. The term "pseudotyped" is a term related to the process of production of the claimed product (a recombinant retrovirus). According to the case law (cf. "Case Law of the Boards of Appeal of the EPO", 9th edition 2019, I.C.5.2.7, 133), process features can establish novelty of the claimed product only if they cause it to have different properties from the products previously described in the art. Thus, it is important to assess which properties are implied by, or associated with, this term.

13.1 Claim 1 specifies that the pseudotyping is performed by using a modified E2 alphavirus glycoprotein which specifically targets DC-SIGN. There is no limitation as regards the type and extent of the modification(s) performed on the native (non-modified) E2 alphavirus glycoprotein from which the modified E2 alphavirus glycoprotein is derived. Claim 1 requires only that the E2 alphavirus glycoprotein resulting from such a modification(s) specifically targets DC-SIGN. Thus, regardless of the modification(s) performed, this is the sole, essential property implied by, and associated with, the term "pseudotyped" in claim 1.

13.2 Since there is no limitation to the type and extent of modifications performed on the native (non-modified) E2 alphavirus glycoprotein, these modifications are not limited to the specific mutations blinding the

canonical binding target HS exemplified in the patent application or to similar/equivalent mutations. They may also comprise other modifications, such as (large) insertions and deletions (indels) within the native (non-modified) E2 alphavirus glycoprotein, or even other modifications of a type completely different. Thus, claim 1 does not clearly exclude pseudotyping with chimeric E2 alphavirus glycoproteins, wherein the DC-SIGN specificity may be associated with a peptide, polypeptide or any other (ligand) molecule, inserted within a native (non-modified) E2 alphavirus glycoprotein and disrupting thereby the specificity of the native (non-modified) E2 alphavirus glycoprotein.

In this context, it is worth noting that the presence of a C-type lectin-like receptor capable of rapid binding and endocytosis of materials in dendritic cells had already been reported in the prior art (cf. paragraph [0223]) and that DC-targeting by antibodies was also known in the art (see Bonifaz *et al.*, J. Exp. Med., 2004, Vol. 199, No. 6, pages 815-824; annexed to appellant's submissions dated 13 December 2013). It is also noted that, according to the patent application, "... some non-specific binding to other molecules ... may occur even if the targeting molecule is specific for DC-SIGN" (cf. page 11, lines 12-15 of the patent application).

13.3 Moreover, although the term "pseudotyped" in claim 1 indicates that the E2 alphavirus glycoprotein is from an alphavirus other than the claimed recombinant retrovirus, the fact that there is no limitation to the type and extent of modifications performed on the native E2 alphavirus glycoprotein renders the source of said glycoprotein irrelevant. The term "pseudotyped" may define the starting (native E2 alphavirus

glycoprotein) material but is silent (except for the required DC-SIGN specificity) on the final (modified E2 alphavirus glycoprotein) product. If only as an extreme case, the E2 glycoprotein from any alphavirus other than Sindbis virus, such as Aura virus, (Western, Venezuelan) equine encephalitis virus, Semliki Forest virus, etc., can always be modified - by carrying out an appropriate number and type (insertions, deletions, substitutions) of modifications - so as to be identical to the native (non-modified) E2 glycoprotein from Sindbis virus. Thus, the claimed retrovirus may also be a recombinant Sindbis virus, wherein the modified E2 alphavirus glycoprotein specifically targets DC-SIGN but all other properties - in particular the amino acid sequence - of said modified E2 alphavirus glycoprotein may be identical to those of a native (non-modified) E2 glycoprotein from Sindbis virus, because the latter glycoprotein can always be prepared or derived from an E2 glycoprotein of any other alphavirus.

14. Whilst abbreviations in a claim may be allowed if they are well-known and accepted in the concerned, relevant technical field, such as for instance HIV, G-CSF, IL, and TNF, this is not the case for the abbreviation DC-SIGN in claim 1. This abbreviation is spelled out, though, and its meaning is clearly defined in the description of the patent application, namely Dendritic Cell Specific ICAM-3 (Intracellular Adhesion Molecules 3)-Grabbing Non-integrin.

Clarity and support by the description

15. In the light of the broad scope of claim 1, the objections raised by the examining division under Articles 84 and 83 EPC are indeed relevant:

15.1 The disclosure of the patent application is not concerned with recombinant retroviruses with DC-specificity provided by chimeric proteins or ligand molecules; this subject-matter - which falls within the scope of claim 1 (*supra*) - is not supported by the patent application. Nor is the patent application concerned with recombinant retroviruses of the nature and properties resulting from a process such as referred to in point 13.3 above and which are related to the recombinant retroviruses described in document (1) (WO 00/61772). This subject-matter however falls also within the scope of claim 1 (*supra*).

15.2 The broad scope of claim 1 renders also relevant the specific objection raised under Article 84 EPC, namely that claim 1 attempts to define the (modified E2 alphavirus) glycoprotein by reference to the result to be achieved (specific DC-SIGN targeting).

16. The arguments of the appellant are based on a narrower understanding of the scope of claim 1 and on the alleged contribution of the patent application to the art, namely that "a pseudotyped retrovirus can be specifically targeted using the E2 glycoprotein itself, rather than *via* an antibody linkage" (underlined by the board), and that the patent application "not only exemplifies one particular way of modifying the E2 glycoprotein, i.e. by providing mutations of the HS binding site of E2, but also teaches the skilled person how equivalent mutations may be obtained" (underlined by the board).

16.1 As stated above, it is questionable whether DC-targeting or specificity *via* an antibody is clearly excluded from the scope of claim 1, and whether the scope of claim 1 is actually limited to mutations

equivalent to those exemplified in the patent application. For the reasons set out above, none of these questions can be answered in the affirmative. There is no reason to read features or limitations into claim 1 which are not present there, but only derivable from the description of the patent application (cf. "Case Law", *supra*, II.A.6.3.4, 312; see also, I.C.4.8, 122).

16.2 It is worth noting that the combination of a lentivirus vector with a modified E2 alphavirus glycoprotein that specifically targets DC-SIGN - and having thus the alleged unexpected advantages referred to by the appellant in the submissions dated 13 December 2013 - falls within the scope of claim 1. Claim 1 is however not limited to this specific combination, but comprises recombinant retroviruses and retroviral vectors of a nature and with properties referred to in point 13.3 above, and which are related to those described in document (1) (WO 00/61772).

17. In view of these considerations, there is no reason to deviate from the findings of the examining division. Thus, the main request does not fulfil the requirements of Article 84 EPC alone or in combination with Article 83 EPC.

18. Against this backdrop, no further questions pose. The impugned decision is to be upheld.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Voyé B. Stolz

Decision electronically authenticated