Internal distribution code:

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

Datasheet for the decision of 22 March 2024

Case Number: T 0197/22 - 3.3.07

Application Number: 17207662.2

Publication Number: 3318248

IPC: A61K9/127, A61K48/00, A61K31/7105, C07H21/02

Language of the proceedings: EN

Title of invention:
DELIVERY OF MRNA FOR THE AUGMENTATION OF PROTEINS AND ENZYMES IN HUMAN GENETIC DISEASES

Patent Proprietor:
Translate Bio, Inc.

Opponents:
Withers & Rogers LLP
Brady, Paul Andrew

Headword:
Delivery of mRNA II/TRANSLATE BIO

Relevant legal provisions:
RPBA 2020 Art. 12(4)
EPC Art. 83

Keyword:
Amendment to case
Sufficiency medical use claim

Decisions cited:
T 0424/21, G 0002/21

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 0197/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 22 March 2024

Appellant: (Patent Proprietor)	Translate Bio, Inc. 200 West Street Waltham, MA 02451 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Opponent 1)	Withers & Rogers LLP 4 More London Riverside London SE1 2AU (GB)
Representative:	Graf von Stosch Patentanwaltsgesellschaft mbH Prinzregentenstraße 22 80538 München (DE)
Respondent: (Opponent 2)	Brady, Paul Andrew Abel & Imray 20 St. Andrew Street London Greater London EC4A 3AG (GB)
Representative:	EIP Fairfax House 15 Fulwood Place London WC1V 6HU (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 16 November 2021 revoking European patent No. 3318248 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	D. Boulois
Members:	M. Steendijk
	L. Basterreix

Summary of Facts and Submissions

I. European patent 3 318 248 ("the patent") was granted on the basis of twenty claims.

Claim 1 as granted related to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and at least one mRNA molecule encoding a peptide or polypeptide, wherein the at least one mRNA molecule is encapsulated in a liposome which has a size of less than 100 nm and comprises one or more cationic lipids, one or more non-cationic lipids, and one or more PEG-modified lipids.

II. Two oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed.

III. The patent proprietor filed the appeal against the decision of the opposition division to revoke the patent.

The decision was based on the main request and auxiliary requests 1-3, all filed on 16 September 2021.

Claim 1 of the main request defined:

"A pharmaceutical composition comprising a pharmaceutically acceptable excipient and at least one mRNA molecule encoding a peptide or polypeptide for use in therapy, wherein the at least one mRNA molecule is encapsulated in a liposome having a size of less than

100 nm, wherein said liposome comprises one or more cationic lipid(s), one or more non-cationic lipid(s), and one or more PEG-modified lipid(s), and wherein said at least one mRNA encodes a functional protein or enzyme."

Claim 1 of auxiliary request 1 additionally defined with respect to claim 1 of the main request that the composition is:

"for use in treating a disease which results from a protein or enzyme deficiency in a subject".

Claim 1 of auxiliary request 2 additionally defined with respect to claim 1 of auxiliary request 1 the features:

"wherein:
a. the subject has an underlying genetic defect that leads to compromised expression of the protein or enzyme; and
b. the at least one mRNA encodes a functional version of the protein or enzyme."

Claim 1 of auxiliary request 3 additionally defined with respect to claim 1 of auxiliary request 1 the features:

"wherein:
a. the subject has an underlying genetic defect that leads to compromised expression of the protein or enzyme;
b. wherein the underlying genetic defect results in (i) non-synthesis of the protein, (ii) reduced synthesis of the protein, or (iii) synthesis of the protein, wherein

the protein lacks or has diminished biological activity; and
c. the at least one mRNA encodes a functional version of the protein or enzyme."

IV. In its decision the opposition division cited *inter alia* the following documents:

D14: European Journal of Pharmaceutics and Biopharmaceutics, 2009, 71,484-489 (published online 10 October 2008)
D15: Antisense Drug Technologies, 2007, 2nd Ed., Chapter 9, Ian MacLachlan, 237-270
D20: WO 90/11092 A1
D39: WO 2012/170930 A1
D48: Science Translational Medicine, 2017, 9, eaaj2300, 1-15
D59: Declaration Dr Anchordoquy dated 4 August 2021
D74: Declaration Dr Anchordoquy dated 22 July 2020

The opposition division arrived at the following conclusions:

(a) The main request did not comply with article 83 EPC. The subject-matter of claim 1 of the main request was drafted as a medical use claim, which required the presence of a therapeutic effect over the whole scope of the claims. Document D39 justified serious doubts that the claimed invention could be practiced over the whole claimed scope for any therapy and any disease. Since a therapeutic effect was not credibly achievable for all diseases resulting from a protein deficiency, showing at least one way of carrying out the invention in the patent was not sufficient to enable the invention as claimed.

(b) Auxiliary requests 1-3 did not comply with Article 83 EPC for the same reasons as the main request.

V. With the statement of grounds of appeal, the patent proprietor upheld the main request and auxiliary requests 1-3 on which the decision under appeal was based.

VI. With the reply to the appeal, opponent 2 objected that a particular argument in the statement of grounds of appeal regarding the sufficient disclosure of a first medical use claim represented an amendment to the proprietor's case, which should not be admitted.

VII. The following additional documents have been cited during the appeal procedure:

A102: EPI letter of 31 January 2000
A103: Minutes of the 81st Meeting of the Administrative Council
A104: PNAS, 2010, 107(5), 1864-1869
A105: J Control Release, 2019, 303, 91-100 (Author manuscript from PMC)
A106: J Pharm Sci, 2011, 100(1), 38-52

A107: Nature Biotechnology,Advance online publication 2011, doi:10.1038/nbt,1733
A108: Gene Therapy, 2000, 7, 1867-1874
A109: Advances in Genetics, Vol. 83, 2005, pages 157-188

A110: Plos One, 2017, 12(10): e0186844
A111: Proprietor's letter of 23 November 2017 in EPA 15767977.0

A112: Proprietor's letter of 13 November 2018 in EPA 12728007.1
A113: Proprietor's letter of 14 August 2017 in EPA 14792713.1
A114: Nat Nanotechnol, 2020, 15(4):313-320 (Author manuscript from PMC)
A115: https://www.proteinatlas.org/ENSG00000130427-EPO/tissue
A116: Opponent's submission in first instance in respect of Articles 54 and 56 EPC of 10 January 2020
A117: Communications Biology, 2020,https://doi.org/10.1038/s42003-021-02441-2
A118: Declaration by Kimberly J Hassett
A119: Drug Metab Dispos, 1998, 26(2): 126-131

A120: Translate Bio, press release 31 July 2019,
A121: Proprietor's submission in first instance of 8 June 2020

A122: Page 600-45, section 608.01 (p), sub-section D of the US Patent and Trademark Office Manual of Patent Examining Procedure (May 1988 edition)
A123: Communication issued by EPO Board 3.3.04 on 2 October 2023 in case T3147/19

The appellant-patent proprietor filed documents A102-A106 with the statement of grounds of appeal, documents A120-A121 with the letter of 31 August 2023 and documents A122-A123 with the letter of 18 January 2024.

Respondent-opponent 1 filed documents A107-A109 with the reply to the appeal.

Respondent-opponent 2 filed documents A110-A119 with the reply to the appeal.

VIII. In its communication pursuant to Article 15(1) RPBA the Board expressed *inter alia* the preliminary opinion that the main request and auxiliary request 1 did not comply with Article 83 EPC.

IX. Oral proceedings were held on 22 March 2024.

X. The arguments of the patent proprietor relevant to the present decision are summarized as follows:

(a) Admittance of arguments and documents

The argument that it is not required for compliance of a claim defining a composition for use in therapy as covered by Article 54(4) EPC with Article 83 EPC to demonstrate utility over the whole scope of the claim for any therapy and any disease, represented a mere development of the argument presented before the opposition division that the patent sufficiently demonstrated one way of carrying out the invention.

Documents A102-A105 were responsive to findings in the decision under appeal. Document A106 was filed in reply to documents D59 and D74 filed by opponent 2 under Rule 116 EPC during the proceedings before the opposition division to support the argument that the discontinuation of a clinical trial does not imply a lack of efficacy. Document A120 was filed in response to the argument by opponent 2 in its reply to the appeal that a product from the patent proprietor falling under claim 1 of the main request ("MRT5005") had failed to show efficacy in clinical trials. Documents A102-A107 and A120 should therefore be admitted into the appeal proceedings.

The documents A107-A115 and A117-A119 lacked relevance and their admittance into the appeal proceedings was not justified.

(b) Sufficiency of disclosure

In line with the established jurisprudence as represented by T 424/21 it was in case of a claim defining a composition for use in therapy as covered by Article 54(4) EPC not required to demonstrate utility over the whole scope of the claim for any therapy and any disease.

Firefly luciferase represented an established reporter protein for demonstrating effective gene transfer and had been used for such purpose in a variety of documents on file, including document D20. The results from examples 7 and 8 in Figures 2-5 of the patent demonstrated with the effective *in vivo* expression of firefly luciferase in mouse hepatocytes that the used liposomes provided for the effective delivery and *in vivo* expression of the contained mRNA. The effective delivery and expression of mRNA encoding a functional protein or enzyme by liposomes as defined in the claims of the main request allowed for the treatment of diseases in which the subject benefits from the provision of the functional protein or enzyme.

Documents D14 and A106 represented evidence that the skilled person was well aware of the concept of gene therapy. With the further guidance in the patent the skilled person was therefore able to match the functional protein with the disease to be treated without any undue burden.

Following the proof of concept regarding the delivery of mRNA and its expression into a functional protein presented in the patent the skilled person would on the basis of the common knowledge and the instructions in the patent routinely optimize the lipid composition and adjust the administered dose of the mRNA to achieve the therapeutically required levels of the expressed functional proteins or enzymes.

Document D39 confirmed the therapeutic utility of the claimed compositions. The levels of expression of mRNA encoding human erythropoietin (hEPO) achieved with such compositions in healthy mice described in document D39 would in accordance with document D48 be effective in the treatment of anemic mice.

XI. The arguments of the opponents relevant to the present decision are summarised as follows:

(a) Admittance of arguments and documents

During the first instance proceedings the patent proprietor had argued that the invention could be practiced across a broad range of therapeutic indications. The patent proprietor's argument that claim 1 of the main request related to the first therapeutic use of the defined composition for which it was not necessary to demonstrate utility in treatment of a plurality of diseases represented an amendment to its case for which no justification had been presented.

The documents A107, A110-A115 and A117-A119 were filed to address the patent proprietor's arguments in its statement of grounds of appeal and should be admitted into the appeal proceedings.

Documents A102-A106 and A120 lacked relevance and their admittance into the appeal proceedings was not justified.

(b) Sufficiency of disclosure

The experiments of examples 7 and 8 of the patent merely demonstrated the unquantified *in vivo* expression in hepatocytes of mRNA for a reporter protein, namely firefly luciferase (FFL). The patent did thereby not demonstrate any therapeutically relevant level of expression of mRNA nor the absence of unacceptable toxicity.

As confirmed by document D14 the luciferase activity in such experiments only indirectly measured protein expression levels. At the same time it was known from document D64 that for instance most antibodies require high and sustained serum levels to achieve therapeutic effects, whereas gene transfer methods typically provided only low levels of expression. The contemporaneous review in document A106 further affirmed that delivery efficiencies of synthetic vectors had been too low to obtain therapeutic levels of gene expression.

Document D39 confirmed that the liposomal compositions as described in the patent did not generally allow for a sufficient level of expression of EPO in mice to achieve actual

therapeutic benefit in the form of a rise in hematocrit levels. Documents A107, A110 and A119 indicated that the lack of an observed rise in hematocrit levels in document D39 could not be attributed to animal model involving healthy mice.

Accordingly, the patent did not sufficiently disclose the claimed invention.

XII. The appellant (patent proprietor) requested that the decision under appeal be set aside, that the requirements of article 83 EPC be held satisfied with respect to the main request and that the case be remitted to the opposition division for examination of the remaining grounds of opposition.

Subsidiarily, the patent proprietor requested that the requirements of article 83 EPC be held satisfied with respect to one of auxiliary requests 1-3 and that the case be remitted to the opposition division for examination of the remaining grounds of opposition.

The patent proprietor further requested that documents A107-A119 not be admitted into the appeal proceedings and that documents A120-A123 be admitted into the appeal proceedings.

XIII. The respondents (opponents) requested that the appeal be dismissed.

Opponent 2 requested that the case be remitted to the opposition division in the event that the main request or any of auxiliary requests 1-3 are considered to comply with article 83 EPC.

Opponent 2 further requested that documents A110-A119 be admitted into the appeal proceedings and that documents A102-A106 and A120-A123 as well as a new argument from the patent proprietor regarding the requirement of sufficient disclosure for a first medical use claim not be admitted into the appeal proceedings.

Reasons for the Decision

1. Admittance of arguments and documents

1.1 The patent proprietor's argument concerning the sufficiency of disclosure of first medical use claims

In the statement of grounds of appeal the patent proprietor argued that sufficiency of disclosure of a claim directed to the so-called first medical use of a composition under Article 54(4) EPC is to be acknowledged if the patent credibly discloses a specific therapeutic utility of the composition and that it is not required to demonstrate utility over the whole scope for any therapy and any disease.

Opponent 2 objected that this argument represented an amendment to the patent proprietor's case, which should not be admitted.

According to the minutes of the oral proceedings before the opposition division (see page 7, second paragraph) the patent proprietor maintained during the first instance proceedings that the claimed invention was sufficiently disclosed, because the patent described at least one way of performing the claimed invention. The Board considers that the patent proprietor's argument

objected to by opponent 2 represents merely a further development of the argument mentioned in the minutes and has therefore acknowledged the argument to be part of the appeal proceedings under Article 12(2) RPBA.

1.2 Document A106

Document A106 was cited by the patent proprietor in response to documents D59 and D74 filed by opponent 2 under Rule 116 EPC during the first instance proceedings in particular to support the patent proprietor's argument that the discontinuation of a clinical trial does not imply a lack of efficacy. Opponent 2 contested the admittance of document A106 for it being late filed and lacking relevance. The Board considers that the filing of document A106 in the appeal proceedings is justified as response to the filing of documents D59 and D74 at a late stage during the first instance proceedings by opponent 2.

The Board has therefore admitted document A106 in the appeal proceedings under Article 12(4) RPBA.

1.3 Documents A107, A110 and A119

Documents A107, A110 and A119 were cited by the opponents in their replies to the appeal to support their arguments that contrary to the proprietor's submissions the lack of an effect of expressed mRNA on the hematocrit level in healthy mice reported in document D39 supported the objection of lack of sufficient disclosure.

The Board considers that the filing of documents A107, A110 and A119 in the appeal proceedings is justified as

response to the proprietor's appeal and that their admittance is not detrimental to procedural economy.

The Board has therefore admitted documents A107, A110 and A119 in the appeal proceedings under Article 12(4) RPBA.

1.4 Documents A102-A105, A108, A109, A111-A115, A117, A118 and A120

In its communication pursuant Article 15(1) RPBA the Board expressed the preliminary opinion that documents A102, A103, A104, A105, A106, A114, A115, A117, A118 and A120 addressed issues possibly relevant to the appeal and that their admittance did not seem detrimental to procedural economy, but that the admittance of documents A108-A109 and A111-A113 did not seem justified.

In line with its preliminary opinion the Board admitted during the oral proceedings documents A102, A103, A104, A105, A106, A114, A115, A117, A118 and A120 and refused to admit documents A108-A109 and A111-A113.

Given the Board's findings on the issue of sufficiency of disclosure concerning the patent proprietor's main and auxiliary requests, which are not affected by the content of these documents (see sections 2 and 3 below), further details for the reasons regarding the admittance and non-admittance of these documents are of no relevance to the decision taken.

2. Main request - Article 83

2.1 The Board agrees with the patent proprietor that in case of a claim for a composition for use under Article

54(4) EPC it is not generally required for compliance with Article 83 EPC that a patent discloses the therapeutic suitability of the defined compositions in treatment of a plurality of diseases (see T 424/21, reasons 40).

However, as claim 1 of the main request defines a composition for use in therapy, the patent must provide the skilled person with sufficient instructions for applying the compositions within the scope of the claim in some form of therapy without undue burden. In line with the considerations in G 2/21 (see reasons 77) this requires that the patent must substantiate the therapeutic utility of the claimed composition if in the absence of experimental data it would not be credible to the skilled person that any therapeutic effect is achieved.

2.2 Claim 1 of the main request defines the composition to comprise mRNA encoding a functional protein or enzyme. The patent demonstrates in examples 7 and 8 with *in vivo* experiments in mice that mRNA encoding firefly luciferase (FFL) may be effectively transfected and expressed using a liposomal transfer vehicle as defined in claim 1 of the main request.

As recognized by the patent proprietor during the oral proceedings, the expression of FFL luciferase serves no purpose in any therapy. According to the proprietor, examples 7 and 8 provided nevertheless with the use of FFL proof of concept that the defined transfer vehicles allowed for the effective transfer and expression of therapeutically useful proteins.

The Board observes that claim 1 of the main request defines the encoded protein merely as a functional

protein or enzyme and leaves the nature of the intended therapy still to be determined. The encoded protein FFL in examples 7 and 8 of the patent may well be considered as a functional protein as defined in the claim, yet the patent provides the skilled person no instruction for the therapeutic use of the mRNA encoding FFL when encapsulated in a transfer vehicle as defined in claim 1 of the main request.

2.3 Even if the term "functional protein or enzyme" in claim 1 of the main request is understood as functionally restricted to a protein with a feasible therapeutic utility, the Board considers that the patent does not provide the skilled person with a sufficient disclosure to generally enable the therapeutic use of the claimed formulation comprising the mRNA encoding for an accordingly defined protein.

2.3.1 The patent provides in Figures 2-5 results from the experiments of examples 7 and 8 in which mice were administered mRNA encoding FFL in a liposomal formulation as defined in claim 1 of the main request. Figure 2 presents results from bioluminescence assays which detect according to paragraph [0123] of the patent the preferential FFL expression in the liver of the treated animals. Figures 3 and 4 presents results from *in situ* hybridisation assays which indicate according to paragraphs [0124]-[0125] of the patent the detection of FFL-mRNA in the liver of treated animals. Figure 5 further presents results from immunohistochemical assays which indicate according to paragraph [0127] of the patent the detection of expressed FFL in the hepatocytes of the treated animals.

2.3.2 Document D14 is a review article on the prospects for mRNA gene delivery published one year before the priority date of the patent. As pointed out by the opponents, document D14 (see page 486, left column, second paragraph) indicates that luciferase assays only provide an indirect measure of protein expression levels. During the oral proceedings, the proprietor maintained that the experimental results reported in the patent demonstrated the effective *in vivo* transfer and expression of FFL-mRNA, but acknowledged that the results reported in the patent do not quantify the actual expression of the transferred mRNA.

2.3.3 Document D64 represents prior art reporting the stable expression of antibodies at therapeutic levels after gene transfer using a viral vector. Document D64 states that most antibodies require high and sustained serum levels. According to document D64 the high antibody concentrations required for clinical efficacy rendered the development of antibody gene transfer technologies challenging, because gene transfer typically achieved only low expression levels (see D64, page 587, right column, second paragraph).

Document A106 represents a review of trends in clinical trials for the delivery of nucleic acid based therapeutics, which was published only shortly after the priority date of the patent. The document reports that as of December 2009 (corresponding to the priority date of the patent) there had been 1579 gene therapy clinical trials worldwide, of which about 25% involved non-viral vectors. In this context the document explicitly states (see page 39, left column, lines 9-14):

"Currently, delivery efficiencies of synthetic vectors in the clinic are too low to obtain therapeutic levels of gene expression."

As explained in section 2.3.2 the patent only provides evidence which indicates a detectable *in vivo* expression of mRNA encoding the reporter protein FFL using liposomes with a constitution as defined in claim 1 of the main request without providing a basis for the quantification of this expression. Documents D64 and A106 indicate, however, that formulations for gene transfer which allowed for the generation of a detectable level of expression of a particular gene still failed to achieve the quantitatively adequate levels of expression required for effective gene therapy. The Board therefore considers that documents D64 and A106 substantiate serious doubts that the patent provides the skilled person with a sufficient disclosure to generally achieve effective therapy using a formulation within the definition of claim 1 of the main request and thus carry out the claimed invention without undue burden.

2.4 The patent proprietor argued that FFL represented an established reporter gene for demonstrating effective gene transfer and that the experimental evidence in the patent provided thereby the crucial proof of concept for the suitability of the defined formulations in gene transfer therapy. Following this proof of concept, the skilled person was according to the proprietor well able on the basis of the instructions in the patent and the common knowledge to optimize the lipid compositions and to adjust the administered dose to achieve the therapeutically required levels of the protein of interest.

The Board observes that in the prior art FFL has indeed been relied upon as an established reporter gene for investigating formulations intended for gene transfer application. For instance, document D20 describes in example 13 experiments with FFL to explore the effect of dose levels and time on the total luciferase extracted from muscle of mice injected with formulations comprising mRNA and DNA encoding FFL. Notably, the experiments involved quantification of the expression as measured in light units using a standard curve established by measuring the light units produced by purified FFL within control muscle extract (see D20, pages 62-62, bridging sentence). However, as explained in section 2.3.3 above, the mere detection of an unquantified level of expression of FFL using a particular formulation for gene transfer does not credibly disclose the general suitability of such a transfer vehicle for use in gene therapy, because in view of documents D64 and A106 serious doubts prevail that such a formulation allows to generally achieve therapeutically effective levels of expression of the contained mRNA. The Board is therefore not convinced that the patent provides actual proof of concept regarding the suitability of the claimed formulations for use in therapy.

The patent refers in paragraphs [0042] and [0087] to parameters which may be modified to optimize transfection efficiency, including the selection of the lipids and their molar ratios as well as the size of the liposomal formulations. Such parameters had also been mentioned in textbooks such as document D15 for the optimization of transfer vehicles for nucleic acids in general (see D15, pages 249-251, section 9.3.5). The patent further indicates in paragraph [0081] that the

compositions may be administered and dosed in accordance with current medical practice. However, the Board considers that without substantiation of the suitability of a formulation for therapy to start with, these suggestions for optimization and dosing remain proposals for a research project which do not overcome the doubts regarding the suitability of the claimed formulations for use in therapy based on documents D64 and A106.

2.5 The patent proprietor further argued that contrary to the finding in the decision under appeal the post-published document D39 did not indicate any lack of therapeutic efficacy, but actually confirmed the therapeutic utility of the claimed formulations.

Document D39 describes in its example 1 lipid nanoparticle compositions containing mRNA encoding human erythropoietin (hEPO), which comprise like the liposomes of claim 1 of the main request a cationic lipid, a non-cationic lipid and a PEG-modified lipid (see D39, pages 37-38, formulations 1-4). Document D39 reports in Table 1 the following observed serum levels of hEPO in CD-1 mice after the administration of these composition (see D39, page 41):

Cationic/Ionizable Lipid Component	Dose of Encapsulated mRNA (ug)	Secreted Human EPO Protein (ng/mL)	Increase in Hematocrit (%)
C12-200	30	18,306	15.0
HGT4003	150	164	0.0
ICE	100	56.2	0.0
DODAP	200	4.1	0.0

Table 1. Raw values of secreted hEPO protein for various cationic lipid-based nanoparticle systems as measured via ELISA analysis (as depicted in **FIG. 8**). Doses are based on encapsulated hEPO mRNA. Values of protein are depicted as nanogram of human EPO protein per milliliter of serum. Hematocrit changes are based on comparison of pre-bleed (Day -1) and Day 10.

Whilst document D39 indicates in Table 1 that only the "C12-200" composition provided sufficient expression of hEPO to increase hematocrit levels in the non-anemic CD-1 mice, even the least effective composition comprising the cationic lipid "DODAP" resulted in a serum concentration of hEPO of 4.1 ng/ml, which was according to document D39 still 30-fold over the normal physiological levels of EPO protein (see D39, page 41, lines 10-14). Document D48 reports the effects of the administration of recombinant hEPO (rhEPO) on renal anemia in adenine-treated mice. The results presented in document D48 indicate that the administration of rhEPO allowed for the recovery of hematocrit levels in these anemic mice (see D48, page 9, Figure 7A). The administered dose in the experiments of document D48 generated a serum level of rhEPO commensurate with the 4.1 ng/ml reported in Table 1 of document D39 for the "DODAP" composition (see D48, page 9, Figure 7J). Taking account of the information in document D48 the Board therefore agrees with the patent proprietor that the results concerning the effect on hematocrit levels in non-anemic mice reported in document D39 do not demonstrate a lack of therapeutic efficacy of the described "DODAP" composition and that the 30-fold increase over normal levels of EPO reported in Table 1 of document D39 rather suggests the therapeutic potential of this composition.

The opponents contended that the lack of an effect on hematocrit levels reported in Table 1 of document D39 nevertheless indicated a lack of therapeutic efficacy of the used compositions in view of documents A107, A110 and A119. However, document A107 describes the effects of the administration of mRNA encoding murine EPO (mEPO) on hematocrit levels in mice (see A107, page 2, Figures 2c and 2d) and thus concerns the effects of

a different protein than the human EPO described in documents D39 and D48. Moreover, documents A110 and A119 describe experiments in anemic mice with a compromised response to EPO (see A110, page 2, final paragraph; see A119, page 126, left column), rather than a deficit in EPO production as in the mice used in document D48. Documents A107, A110 and A119 are therefore not considered to support the opponents' contention.

However, whilst document D39 thus may describe with the mentioned experimental results the *in vivo* expression of the administered mRNA encoding hEPO in a quantity which could indicate the described compositions to be therapeutically useful, the patent fails to disclose such a quantitatively adequate expression of mRNA from the compositions as defined in claim 1 of the main request. In accordance with the considerations in G 2/21 (see reasons 77) a lack of sufficiency of disclosure cannot be remedied by post-published evidence. The patent proprietor's argument relying on the post-published document D39 is therefore not considered persuasive.

2.6 Accordingly, the Board concludes that the main request does not comply with Article 83 EPC.

3. Auxiliary requests

3.1 Auxiliary request 1

Claim 1 of auxiliary request 1 more specifically defines with respect to claim 1 of the main request the therapeutic use of the defined composition in treating a disease which results from a protein or enzyme deficiency in a subject.

Auxiliary request 1 retains the definition of the mRNA as encoding a functional protein or enzyme of the main request. This definition of the mRNA results in the non-compliance of the main request with Article 83 EPC for the reasons as presented in sections 2.2 and 2.3 above. The additional specification of the therapeutic use in claim 1 of auxiliary request 1 does not change the definition of the mRNA. Auxiliary request 1 does therefore not comply with Article 83 EPC for the same reasons as the main request.

3.2 Auxiliary requests 2 and 3

Auxiliary requests 2 and 3 additionally define in claim 1 with respect to claim 1 of auxiliary request 1 that the subject has an underlying genetic defect leading to compromised expression of the protein or enzyme and that the mRNA in the composition encodes a functional version of the protein or enzyme.

Auxiliary requests 2 and 3 thereby restrict the definition of the functional protein or enzyme encoded by the mRNA to the actual deficient protein or enzyme giving rise to the disease to be treated. The reason for non-compliance of the main request presented in section 2.2 above does therefore not apply.

However, as explained in section 2.3 documents D64 and A106 indicate, that systems for gene transfer which allowed for the generation of a detectable level of expression of a particular gene still failed to achieve the quantitatively adequate levels of expression required for effective gene therapy, whereas the patent only provides evidence for detectable *in vivo* expression of mRNA encoding the reporter protein FFL.

As the definition of the encoded protein or enzyme in auxiliary requests 2 and 3 remains of a general and purely functional nature documents D64 and D106 thereby also substantiate serious doubts that the patent provides the skilled person with a sufficient disclosure to generally achieve effective therapy using the mRNA encoding a protein or enzyme as defined in claim 1 of the auxiliary requests 2 and 3.

Auxiliary requests 2 and 3 do therefore also not comply with Article 83 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

B. Atienza Vivancos D. Boulois

Decision electronically authenticated