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Datasheet for the decision of 7 March 2024

Case Number: T 1302/21 - 3.3.07

Application Number: 10835016.6

Publication Number: 2506857

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 I/TRANSLATE BIO

Relevant legal provisions:
EPC Art. 123(2)
RPBA 2020 Art. 13(2)

Keyword:
Amendments - added subject-matter (yes)
Amendment after summons - cogent reasons (no)

Decisions cited:
T 1621/16, T 3035/19

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Case Number: T 1302/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 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)
Appellant: (Opponent 1)	Withers & Rogers LLP 4 More London Riverside London SE1 2AU (GB)
Representative:	Graf von Stosch Patentanwaltsgesellschaft mbH Prinzregentenstraße 22 80538 München (DE)
Appellant: (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:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 16 July 2021 concerning maintenance of the European Patent No. 2506857 in amended form.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent 2 506 857 ("the patent") was granted on the basis of twenty claims.

Claim 1 as granted defined:

"A pharmaceutical composition for use in a method of treating a disease in a subject which results from a protein deficiency, the pharmaceutical composition comprising:

a transfer vehicle and at least one mRNA molecule encoding said protein,

the transfer vehicle comprising one or more cationic lipid(s), one or more non-cationic lipid(s), and one or more PEG- modified lipid(s),

wherein the transfer vehicle is a liposome and the size of the transfer vehicle is less than 100 nm,

wherein the pharmaceutical composition preferentially distributes into liver cells after administration to the subject and the encoded protein is expressed in the liver cells of the subject."

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.

The patent proprietor and opponents 1 and 2 filed appeals against the interlocutory decision of the opposition division that the patent as amended in accordance with auxiliary request 2 met the requirements of the EPC.

The decision was based on the main request and auxiliary request 1, both filed on 15 April 2019, and on auxiliary request 2 submitted during the oral proceedings held on 12 January 2021.

The claims of the main request corresponded to the claims as granted except for the deletion of claim 20 as granted.

Amended claim 1 of auxiliary request 1 more specifically defined that the pharmaceutical composition distributes preferentially to hepatocytes and the encoded protein is expressed in the hepatocytes of the subject.

Amended claim 1 of auxiliary request 2 more specifically defined with respect to claim 1 of auxiliary request 1 that the pharmaceutical composition is for use in a method of treating a disease in a subject which results from a protein deficiency, wherein the disease is caused by defects in a liver-specific gene product.

In its decision the opposition division cited *inter alia* the following document:

D17: Gene Therapy (2008) 15, 1193-1199
D18: Antisense Drug Technology:
Principles, Strategies, and Applications, 2nd Edition, 2007, Chapter 9: Liposomal Formulations for Nucleic Acid Delivery (Ian MacLachlan), 237-270

III. The opposition division arrived at the following conclusions:

(a) The main request did not comply with Article 123(2) EPC, because the application as originally filed did not disclose the feature of the size of the transfer vehicle of less than 100 nm in combination with the features of preferential distribution in liver cells and the encoded protein being expressed in the liver cells.

(b) Auxiliary request 1 complied with Article 123(2) EPC. In view of the information in document D17 the selection of the specific size value of <100 nm was convergent with the limitation to hepatocytes.

Claim 1 of auxiliary request 1 did not comply with Article 83 EPC.

(c) The additional feature in claim 1 of auxiliary request 2 was already present in claims 14 and 15 as granted. A late filed objection under Article 84 EPC was not admitted.

The additional feature in claim 1 of auxiliary request 2 found its basis in the application as filed. Auxiliary request 2 further complied with the requirement of Article 123(2) EPC for the same reasons as auxiliary request 1.

Auxiliary request 2 also complied with the requirements of sufficiency of disclosure, novelty and inventive step.

IV. With the statement of grounds of appeal the patent proprietor upheld the main request on which the decision under appeal was based and filed auxiliary requests 1-35. With the reply to the appeals by the

opponents the patent proprietor additionally filed auxiliary requests 36-71.

V. In its communication pursuant to Article 15(1) RPBA the Board expressed *inter alia* the preliminary opinion that the combination of the selection of a size of less than 100 nm for the transfer vehicle and the definition of preferential delivery and expression of the mRNA in the liver could not be directly and unambiguously derived from the application as originally filed and that the amendment replacing "liver cells" by "hepatocytes" would not overcome this objection.

VI. With the letter of 18 January 2024 the patent proprietor upheld the main request and only maintained auxiliary requests 1, 4, 5, 18, 19, 22, 23, 36, 37, 40, 41, 54, 55, 58 and 59 as previously filed as the renumbered auxiliary requests 1-15.

Claim 1 of the main request corresponds to claim 1 as granted. Claim 1 in auxiliary requests 2, 8 and 10 is identical to claim 1 as granted.

Claim 1 in auxiliary requests 1, 3, 9 and 11 corresponds to claim 1 as granted except for the feature that the defined pharmaceutical composition: "preferentially distributes to hepatocytes after administration to the subject and the encoded protein is expressed in the hepatocytes of the subject."

Claim 1 in auxiliary requests 4, 6, 12 and 14 corresponds to claim 1 as granted except for the feature that the pharmaceutical composition is more specifically defined to be:
"for use in a method of treating a disease in a subject which results from a protein deficiency, wherein the

disease is caused by defects in a liver-specific gene product".

Claim 1 in auxiliary requests 5, 7, 13 and 15 corresponds to claim 1 of auxiliary request 1 with the further definition, as in auxiliary request 4, that the disease is caused by defects in a liver-specific gene product.

VII. In the letter of 21 January 2024 opponent 2 objected that the statement by the patent proprietor in the letter of 18 January 2024 concerning the passage of the liposomes through the liver fenestrae regardless of species represented a new allegation of fact which should not be admitted into the appeal proceedings.

With this letter opponent 2 also filed the following document:

A120: Comparative Hepatology, 2002, volume 1, Article 1

VIII. In the letter of 13 February 2024 the patent proprietor objected that the reliance by opponent 2 on document A120 represented an amendment to the opponent's appeal case which should not be admitted into the appeal proceedings.

With this letter the patent proprietor filed auxiliary requests 16-31. The wording of claim 1 in auxiliary requests 1-16 corresponds respectively to the wording of claim 1 in the main request and auxiliary requests 1-15 except that the subject is further defined as a human subject.

IX. Oral proceedings were held on 7 March 2024.

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

The submission in the patent proprietor's letter of 18 January 2024 regarding the size limitation of less than 100 nm permitting passage of the liposomes through the liver fenestrae regardless of species merely further developed the consideration in the decision under appeal that in view of the information in document D17 the selection of the specific size value of <100 nm is convergent with the limitation to delivery and expression in hepatocytes. This submission did therefore not represent an amendment to the patent proprietor's appeal case.

The filing of document A120 represented a late and unjustified amendment to the appeal case of opponent 2. This amendment should therefore not be admitted into the appeal proceedings.

The application as originally filed specifically explained the importance of the liver as a target organ and expressed a general preference for delivery of the synthetic mRNA and its expression *in vivo* in the liver and in particular the hepatocytes, in the discussion following the presentation of the *in vivo* experiments.

The application as originally filed disclosed for the transfer vehicle a size of less than 100 nm as part of a list of converging preferred options. The size of less than 100 nm was further indicated as preferred in the introduction of example 1, which presented the example as generally illustrating a process for preparing formulations of liposomes with a size of <100 nm.

In line with the common general knowledge expressed in document D18 as well as the information in document D17 relied upon in the decision under appeal the teaching in the application as filed that the liposomal transfer vehicle may for the purpose of targeting hepatocytes be sized such that its dimensions are smaller than the fenestrations in the liver was consistent with the definition of a size of less than 100 nm. This teaching therefore provided a further pointer to the defined combination of features.

The limitation to the delivery and expression in the the subject's liver, in particular the subject's hepatocytes, together with the definition of the size of the liposomes of less than 100 nm thus corresponded to the single selection of the size of the liposomes from a list of convergent options to which the application as originally filed provided specific pointers. In line with the considerations in T 1621/16 no information extending beyond the content of the application as originally filed was thereby generated.

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

The patent proprietor's submissions of 18 January 2024 comprised the new allegation of fact that the size limitation of less than 100 nm permits passage of the liposomes through the liver fenestrae regardless of species.

The filing of document A120 represented a justified response to this new allegation of fact, because it showed that for instance the liver fenestrae in sheep have a diameter substantially below 100 nm.

The application as originally filed did not specifically disclose the combination of the feature regarding the preferential delivery and expression of the mRNA in the subject's liver or hepatocytes with the feature of the size of the liposomal transfer vehicle of less than 100 nm.

The application as originally filed disclosed the relevance of the size of the liposomal transfer vehicle for targeting the delivery of the mRNA. In this context the application as filed referred to the liver only as one target amongst others and explicitly described liposomal transfer vehicles with a large size to avoid delivery to hepatocytes alternatively to transfer vehicles specifically targeting hepatocytes.

The reference in the introduction to the examples to the preparation of liposomes of a size less than 100 nm did not imply a general preference for such a size limitation and was unrelated to the preferential delivery and expression of the contained mRNA to the liver or hepatocytes. The discussion following the *in vivo* experimental results presented in examples 7 and 8 regarding the delivery to the liver and in particular the hepatocytes made no mention of a size requirement for the liposomes of less than 100 nm.

The *in vivo* experiments in the application as originally filed were carried out on mice and the average size the liposomes used in the experiments was actually reported as 68.0 nm, which provided no pointer to the combination of the definition of the size of less than 100 nm for the liposomes and the targeting of the liver or the hepatocytes of the subject.

Documents D17 and D18 could not provide a basis in the application as originally filed for the combination of features regarding the size of the liposomes of less than 100 nm and the targeting of the liver or the hepatocytes in the subject.

XII. The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained on the basis of:

- the main request corresponding to claims 1-19 as granted (claim 20 as granted having been deleted),

- auxiliary requests 1-15, corresponding respectively to auxiliary requests 1, 4, 5, 18, 19, 22 and 23 filed with the statement of grounds of appeal and to auxiliary requests 36, 37, 40, 41, 54, 55, 58 and 59 filed with the reply to the appeals by the opponents.

The patent proprietor further requested that the new submission of 31 January 2024 by opponent 2 relying on document A120 not be admitted, or else that new auxiliary requests 16-31 as filed on 13 February 2024 be admitted.

XIII. The appellant-opponents requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Opponent 1 further requested that the auxiliary requests not be admitted.

Opponent 2 further requested that document A120 be admitted and the patent proprietor's new submission of 18 January 2024 concerning the basis for the definition

of the transfer vehicle size of less than 100 nm and auxiliary requests 16-31 not be admitted.

Reasons for the Decision

1. Admittance - submission of 18 January 2024

The patent proprietor argued in the statement of grounds of appeal (see pages 3-5, section 4) regarding the combination of the size of the liposomal transfer vehicle and the definition of the delivery and expression of the mRNA in the liver that the application as originally filed disclosed the liver as a preferred target organ, in view of which the limitation to a size of the liposomal transfer vehicles of less than 100 nm remained a single selection from a list. This selection was consistent with the disclosure in the application as filed that the liposomal transfer vehicle may be sized such that its dimensions are smaller than the fenestrations of the endothelial layer lining hepatic sinusoids and the reference in example 1 to a size of the transfer vehicle of less than 100 nm.

The patent proprietor's reply to the appeals by the opponents (see page 34-38, section 8) relied with respect to the basis for the combination of the delivery and expression in the liver and the size of the transfer vehicle of less than 100 nm on the submissions in the statement of grounds of appeal and referred with respect to the targeting of hepatocytes to the disclosure of hepatocytes as specific examples of targeted liver cells.

In the letter of 27 March 2023 (see page 2, sections 3.2-3.3) the patent proprietor maintained that the definition of the size of the liposomal transfer

vehicle of less than 100 nm only represents a single selection from a list of converging options and argued that the application as filed provided pointers towards this size limitation. As recognized in the decision under appeal, the general guidance in the application as filed concerning liposomes with a size smaller than the liver fenestrations immediately suggested a size smaller than 100 nm in view of common general knowledge. Moreover, the reference to an illustrative process for preparing mRNA containing liposomes with a size of less than 100 nm in example 1 provided a further pointer. As set out in T 1621/16 a limitation from a list of converging options would not necessarily amount to an undisclosed selection.

Following the Board's communication pursuant Article 15(1) RPBA the patent proprietor reiterated in the letter of 18 January 2024 (see pages 3-5, sections 3.2-3-10) the previously submitted arguments. In addition, the patent proprietor relied in this letter (see page 5, section 3.12) for the first time during the appeal proceedings on the following statement of fact:
"A size limitation of less than 100 nm permits passage of the liposomes through the liver fenestrae, regardless of species."

This new statement of fact thus represents an amendment to the patent proprietor's appeal case under Article 13(2) RPBA.

The new statement of fact was presented in response to the Board's communication. However, regarding the size of the liver fenestrae in different species this communication merely referred to the argument in the statement of grounds of appeal by opponent 2 that

according to document D17 the actual size of the endothelial fenestrae in the liver may significantly vary depending on the species. No new issue regarding the definition of size of the defined liposomes had thus been presented by the opponents or raised by the Board that justified the filing of the new statement of fact by the patent proprietor at the late stage of the proceedings.

In the absence of exceptional circumstances justified with cogent reasons the Board has therefore decided not to admit the above identified statement submitted with the patent proprietor's letter of 18 January 2024 into the appeal proceedings.

2. Admittance - document A120

Document A120 was filed by opponent 2 in the letter of 31 January 2024 in response to the statement in the patent proprietor's letter of 18 January 2024 concerning the size of less than 100 nm permitting passages of the liposomes through the liver fenestrae, regardless of species.

The filing of document A120 thus represented a late amendment to the appeal case by opponent 2 covered by the provision of Article 13(2) RPBA.

Following the decision not to admit the relevant statement in the patent proprietor's letter of 18 January 2024 the Board recognizes no exceptional circumstances that would justify the admittance of document A120.

Accordingly, the Board has decided not to admit document A120 into the appeal proceedings.

3. Main request - Article 123(2) EPC

3.1 Claim 1 of the main request defines the feature of preferential distribution of the composition into liver cells and expression of the encoded protein in the liver cells of the subject together with the feature of the size of the transfer vehicle of less than 100 nm.

This claim thereby includes the information that the defined transfer vehicles with a size of less than 100 nm allow for the preferential delivery and expression of the mRNA in the liver and thus the targeting of the composition to liver cells.

3.2 Concerning the size of the liposomal transfer vehicles the application as originally filed (see page 27, lines 18-20) explicitly teaches:

"Selection of the appropriate size of the transfer vehicle must take into consideration the site of the target cell or tissue (...)".

In this context, the original disclosure (see page 27, line 20 to page 28, line 17) indicates that it may be desirable to limit transfection to certain cells or tissues and describes the liver as an example of an important target organ. The original disclosure mentions that accordingly to target for example hepatocytes a liposomal transfer vehicle may be sized such that its dimensions are smaller than the fenestrations of the entdothelial layer lining the hepatic sinusoids in the liver. The application as filed further describes that alternatively the

liposomal transfer vehicle may be sized such that its dimensions are larger than these fenestrations to limit distribution to hepatocytes.

In the immediately following passage the application as filed (see page 28, lines 8-11) states:

"Generally, the size of the transfer vehicle is within the range of about 25-250 nm, preferably less than about 250nm, 175nm, 150nm, 125nm, 100nm, 75nm, 50nm, 25nm or 10nm."

The skilled person cannot directly and unambiguously derive from this section of the original disclosure that the defined transfer vehicles with a size of less than 100 nm allow for the targeting of liver cells, because this section of the original disclosure fails to disclose the link between this specific size limit of 100 nm for the transfer vehicle and liver cells as target for the defined composition.

3.3 The application as originally filed (see page 39, lines 25-27) indicates that Example 1 illustrates a process for the preparation of small sized (< 100 nm) liposomal formulations. However, this reference to the preparation of liposomal formulations with a size of less than 100 nm is not related to the targeting of liver cells.

The application as originally filed further mentions as part of the discussion of the experimental results (see page 49, line 26 to page 50, line 16) that mRNA encapsulated in lipid-based material can be used for the delivery and expression of genes *in vivo* in liver, in particular hepatocytes. In this discussion regarding the delivery and expression of genes in liver cells no

mention is made of a required size of the liposomal transfer vehicle of less than 100 nm. As pointed out by the opponents, the application as originally filed (see page 46, lines 14-16) actually reported that the formulations used for the *in vivo* experiments to demonstrate the effective delivery and expression of mRNA in liver cells in a mice model involved liposomes with an average size ("Z_{ave}") of less than 68.0 nm.

These passages in the examples relied upon by the proprietor do therefore not provide any pointer to the combination of a size of less than 100 nm of the transfer vehicle and their targeting to the liver.

Even if the skilled person would conclude from the information provided in relation to the examples that liposomes with a size of less than 100 nm as well as the targeting of liver cells represented originally disclosed preferred embodiments, the skilled person could not without such pointer directly and unambiguously derive the combination of these embodiments from the original disclosure.

Accordingly, the information that the defined transfer vehicles with a size of less than 100 nm allow for the targeting of liver cells cannot be directly and unambiguously derived from the mentioned passages in examples.

3.4 The patent proprietor additionally argued that with the common knowledge expressed in document D18 or the information in document D17 referred to in the decision under appeal (see page 8, section 6.3) the skilled person would understand that the targeting of liver cells by a liposomal transfer vehicle with dimensions smaller than the fenestrations in the liver was

consistent with and thereby provided a further pointer to the claimed transfer vehicles with a size of less than 100 nm.

Document D17 (see page 1193, abstract and page 1194, Figure 1) indicates that the dimensions of the endothelial fenestrae are in humans without liver pathology 107 ± 1.5 nm and that these dimensions significantly vary between species.

Document D18 states that for encapsulating nucleic acid the method involving stepwise ethanol dilution generates small (diameter <100 nm), well-defined, stable systems with high encapsulation efficiencies that exhibit the extended circulation lifetimes required to achieve preferential accumulation at target sites such as solid tumors or liver (see D18, page 251, lines 17-21). Document D18 further states that charge neutral carriers of appropriate size can pass through the fenestrated epithelium found in sites of clinical interest such as tumors, sites of infection, inflammation, and in the healthy liver and may accumulate via “passive” targeting if the carriers have a sufficiently small diameter on the order of 100 nm and have extended circulation lifetimes (see D18, page 254, section 9.5).

The Board does not recognize that taking account of this information from documents D17 or D18 the teaching in the patent regarding the targeting of liver cells by liposomal transfer vehicles with dimensions smaller than the fenestrations in the liver implies, as a matter of necessary consequence, that liposomes with a size of less than 100 nm will target liver cells as defined in claim 1 of the main request.

In this context the Board observes that the common general knowledge may be relied upon for assessment of what the skilled person may derive directly and unambiguously from the original disclosure, but cannot compensate for what might be obvious, but has not been disclosed in the application as originally filed itself (see T 3035/19, point 1.7.3 of the reasons).

3.5 According to the considerations in T 1621/16 (see reasons 1.7.3) a claim amended on the basis of multiple selections from lists of converging alternatives may comply with Article 123(2) EPC if the subject-matter resulting from the multiple selections is not associated with an undisclosed technical contribution, and the combination is supported by a pointer in the application as filed.

In view of the above discussed passages in the application as originally filed the Board is of the opinion that the defined preferential delivery and expression in the liver does not represent a selection from a list of converging options, that its combination with the selection of transfer vehicles of a size of less than 100 nm generates the undisclosed technical information that the defined transfer vehicles with a size of less than 100 nm provides for the targeting of liver cells and that the application as originally filed provides no pointer to this combination.

The considerations in T 1621/16 have therefore no pertinence for the assessment in the present case.

3.6 Accordingly, the Board concludes that the main request does not comply with Article 123(2) EPC.

4. Admittance - Auxiliary requests 1-15

Auxiliary requests 1-15 were filed by the patent proprietor with the statement of grounds of appeal and the reply to the appeals by the opponents and subsequently renumbered.

Auxiliary requests 1 and 5 correspond to auxiliary requests 1 and 2 on which the decision under appeal was base and are therefore considered part of the proceedings.

The filing of auxiliary requests 2-4 and 6-15 is considered justified in view of the patent proprietor's explanations in the statement of grounds of appeal (see pages 14-15, section 8) and reply (see pages 39-41, section 11). The Board has therefore admitted these requests under Article 12(4) RPBA.

5. Auxiliary requests 1

Claim 1 of auxiliary request 1 defines with respect to claim 1 of the main request more specifically that the composition preferentially distributes to hepatocytes and that the encoded protein is expressed in hepatocytes of the subject.

Claim 1 of auxiliary request 1 thereby includes the information that the defined transfer vehicles with a size of less than 100 nm allow for the preferential delivery and expression of the mRNA in the hepatocytes and thus the targeting of the composition to hepatocytes.

The patent proprietor relied for the basis of claim 1 of auxiliary request 1 in the application as originally

filed on the same passages as discussed in section 3 in relation to claim 1 of the main request.

The Board observes that the application as filed describes in these passages hepatocytes as examples of liver cells that may be targeted by providing liposomal vehicles of dimensions smaller than the fenestrations of the endothelial layer lining hepatic sinusoids. However, for the same reasons as set out in section 3 in relation to claim 1 of the main request the combination of the targeting of the hepatocytes and the size of the liposomal transfer vehicle of less than 100 nm cannot be directly and unambiguously derived from these passages in the application as originally filed.

Accordingly, the Board concludes that the auxiliary request 1 does not comply with Article 123(2) EPC.

6. Auxiliary requests 2-15

The definition of the subject-matter in claim 1 of auxiliary requests 2-15 includes the same combination of the feature of the targeting of liver cells or hepatocytes together with the feature of the size of the transfer vehicle of less than 100 nm as discussed in sections 3 and 4 above in relation to claim 1 of the main request and claim 1 of auxiliary request 1.

Auxiliary requests 2-15 do therefore not comply with Article 123(2) EPC for the same reasons as set out for the main request and auxiliary request 1.

7. Auxiliary requests 16-31

The patent proprietor conditionally requested the consideration of auxiliary requests 16-31 in case document A120 was admitted into the appeal proceedings.

Following the Board's decision not to admit document A120 auxiliary requests 16-31 are therefore not part of the appeal proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos D. Boulois

Decision electronically authenticated