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Datasheet for the decision of 26 January 2015

Case Number: T 0399/11 - 3.3.08

Application Number: 01129274.5

Publication Number: 1197567

IPC: C12Q1/68, C12N15/63

Language of the proceedings: EN

Title of invention:
Characterisation of gene function using double stranded RNA inhibition

Patent Proprietor:
Devgen NV

Opponent:
BASF SE

Headword:
dsRNA feeding delivery method RNAi/DEVGEN

Relevant legal provisions:
EPC Art. 123(2), 83
EPC R. 114(2)
RPBA Art. 12(4), 13(1)

Keyword:
Main Request - admissibility (yes);
Main Request - added subject-matter (no)
Main Request - sufficiency of disclosure (yes)
Main Request - priority entitlement (yes)
Main Request - novelty and inventive step (yes)
Admissibility fresh case (no)

Decisions cited:

Catchword:

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Case Number: T 0399/11 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 26 January 2015

Appellant I: (Patent Proprietor)	Devgen NV Technologiepark 30 9052 Gent-Zwijnaarde (BE)
Representative:	White, Nina Louise Boult Wade Tennant Verulam Gardens 70 Gray's Inn Road London WC1X 8BT (GB)
Appellant II: (Opponent)	BASF SE 67056 Ludwigshafen (DE)
Representative:	Patzelt, Andrea BASF SE GVX/B - C 6 Carl-Bosch-Straße 38 67056 Ludwigshafen (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 7 December 2010 concerning maintenance of the European Patent No. 1197567 in amended form.**

Composition of the Board:

Chairman	M. Wieser
Members:	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 197 567 was opposed on the grounds of Articles 100(a) and (b) EPC. The opposition division considered that the Main Request (claims as granted) was not entitled to the first priority date claimed (3 July 1998) and thus not novel over document D4 (publication date 29 October 1998; *infra*). Auxiliary Request I was considered to contravene Article 83 EPC. The patent was maintained by the opposition division on the basis of an Auxiliary Request II, filed at oral proceedings on 21 October 2010, and a description adapted thereto.

Claim 1 of this Auxiliary Request II read as follows:

"1. A method of introducing dsRNA or DNA capable of producing dsRNA into a non-human animal which method comprises feeding said animal with a bacterial or yeast cell comprising an expression vector comprising two promoters oriented relative to a DNA sequence such that they are capable of initiating transcription of said DNA sequence to double stranded RNA upon binding of an appropriate transcription factor to said promoters."

II. Notices of appeal were filed by the patentee and the opponent (appellants I and II, respectively).

With its statement setting out the Grounds of Appeal, appellant I maintained, as its Main Request, the claims as granted and it further filed an Auxiliary Request I.

With its statement setting out the Grounds of Appeal, appellant II filed new documentary evidence (documents D15-D20, *infra*).

III. The appellants replied to each other's Grounds of Appeal.

Appellant I withdrew its former requests and filed a new Main Request, Auxiliary Requests I to III and new documentary evidence (documents D21-D25, *infra*).

IV. The board summoned the appellants to oral proceedings and, in a communication pursuant to Article 15(1) of the Rules of the Boards of Appeal (RPBA), informed them of its preliminary, non-binding opinion on the relevant issues of the case.

V. Both appellants replied to the communication of the board.

Appellant I made the former Auxiliary Request III its Main Request and filed a new Auxiliary Request I.

VI. Oral proceedings took place on 26 January 2015 in presence of both appellants.

VII. Claim 1 of the **Main Request** reads as follows:

"1. A method of introducing dsRNA or DNA capable of producing dsRNA into a non-human animal which method comprises feeding said animal with a bacterial or yeast cell comprising an expression vector comprising a DNA sequence located between two promoters capable of initiating transcription of said DNA sequence to double stranded RNA upon binding of an appropriate transcription factor to said promoters."

Claims 2 to 12 were directed to preferred embodiments of the method of claim 1.

VIII. The following documents are referred to in this decision:

D4: L. Timmons and A. Fire, Nature, Vol. 395, 29 October 1998, page 854;

D5: P.M. Waterhouse et al., Proc. Natl. Acad. Sci. USA, Vol. 95, November 1998, pages 13959 to 13964;

D11: M. Stam et al., The Plant J., Vol. 12, No. 1, 1997, pages 63 to 82;

D12: M.K. Montgomery and A. Fire, Trends in Genetics, Vol. 14, No. 7, July 1998, pages 255 to 258;

D15: R. Rajagopal et al., J. Biol. Chem., Vol. 277, No. 49, 6 December 2002, pages 46849 to 46851;

D16: D.P. Walshe et al., Insect Mol. Biol., Vol. 18, No. 1, 2009, pages 11 to 19;

D19: O. Terenius et al., J. Insect Phys., Vol. 57, 2011, pages 231 to 245;

D20: S. Xiang et al., Nature Biotech., Vol. 24, No. 6, June 2006, pages 697 to 702;

D21: H. Tian et al., PLoS ONE, Vol. 4, No. 7, July 2009, e6225, pages 1 to 13;

D22: L. Rodríguez-Cabrera et al., Environmental Microbiol., 2010, doi:10.1111/j. 1462-2920.2010.02259.x;

D23: H. Huvenne and G. Smagghe, J. Insect Phys., Vol. 56, 2010, pages 227 to 235;

D24: H. Guo et al., Gene Therapy, Vol. 18, 2011, pages 95 to 105;

D25: R.R. Isberg and J.M. Leong, Proc. Natl. Acad. Sci. USA, Vol. 85, September 1988, pages 6682 to 6686.

IX. The submissions of appellant I (patentee), insofar as they are relevant to the present decision, may be summarized as follows:

Main Request
Article 100(c) EPC; Article 123(2) EPC

In its Grounds of Appeal, appellant II raised a sole objection under Article 123(2) EPC concerning the location of the DNA sequence in respect of the two promoters. This objection did not apply to the Main Request. The decision of the opposition division concerning the feature "*two identical promoters*" was not contested by appellant II but only by the board in its communication pursuant to Article 15(1) RPBA. This new objection was thus not admissible, the less so since the wording of claim 1 was reproduced *verbatim* in the application as filed.

The contribution of the invention was the (feeding) method of delivery and not the specific DNA vector used in the claimed method. This was reflected at the beginning of the application with reference to "*each aspect of the invention*" and to a "*suitable DNA vector*" (page 3, line 19 of the application as filed) which was defined on page 4, lines 1-3. Accordingly, the same DNA vector defined by the same wording was disclosed for different embodiments (see page 6, lines 1-5 and page 7, lines 1-4). This was also reflected in

the claims as originally filed, in particular in claim 73 relating to a feeding method and referring back to the vector of any of claims 60-67. The vector of claim 60, defined as "*comprising a promoter or promoters*", could be used in any of the methods of the preceding claims. The methods of claims 5, 28 and 39 used a vector with two promoters without requiring them to be identical.

On page 8, lines 9-16 of the application as filed the presence of two identical promoters was defined as a "*further aspect of the invention*", i.e. a specific embodiment. This feature was not disclosed as being essential and generally required. Claim 1 already required to initiate the transcription of the DNA sequence in both directions.

Article 100(b) EPC; Article 83 EPC
Admissibility of documents D15-D20 and D21-D25

With its Grounds of Appeal, appellant II had submitted documents D15-D20 in order to support an objection raised under Article 83 EPC. However, objections under this article had already been raised at the beginning of the opposition proceedings and thus, these documents could have been filed at an earlier stage of the proceedings. If they were admitted into the proceedings, it was then fair to admit also documents D21-D25 filed in direct reply thereto.

Sufficiency of disclosure

The teachings of the patent were appropriate for all animals, including higher animals. The uptake of nutrients (including DNA) *via* the gut was a mechanism common to all animals. *C. elegans* was a model animal

showing such uptake. The *C. elegans* (*nuc-1*) mutant was preferred over wild-type *C. elegans* for reasons disclosed in the patent. Post-published document D4 showed the claimed delivery method to be successfully used with wild-type *C. elegans*.

Documents D17-D18 were not relevant because they were concerned with protozoan parasites, not with animals. Document D15 referred only to preliminary experiments without disclosing any feeding conditions and/or parameters used. This disclosure did not meet the standard required by the case law of the Boards of Appeal. Documents D21-D22, albeit not using *Spodoptera litura* as document D15, showed the claimed feeding method to be successfully used in *S. exigua* and *S. frugiperda*. None of documents D16 and D19-D20 raised serious doubts on the reproducibility of the claimed method. On the contrary, apart from some anecdotal failures, they showed the feasibility of the claimed method and referred thereto as a powerful tool, although with limitations known to be associated with RNA interference (RNAi), such as the variability of inhibition depending on the target gene used. These limitations did not arise from deficiencies of the claimed feeding method but from other factors of RNAi in general, as shown in document D23. Document D24 showed that, when using a naturally invasive *Salmonella typhimurium* bacteria, the *Inv* gene used in document D20 for non-invasive *E. coli*, was not essential for feeding the bacteria to mammals. Document D24 also showed that the *Hly* gene was not essential for dsRNA delivery into mammals but only for improving RNAi efficiency. These post-published documents showed that the feeding method for dsRNA delivery was feasible and that it could also be optimized (as exemplified in the patent by using the *C. elegans* (*nuc-1*) mutant).

Articles 87-89 EPC; Priority

The wording of claim 1 used to characterize the expression vector was found *verbatim* in the first priority document. Claim 1 had thus a formal basis in this first priority document.

Article 100(a) EPC; Articles 54 and 56 EPC

No objections were raised under these articles against the Auxiliary Request II upheld by the opposition division which was broader in scope than the Main Request in appeal proceedings. They were raised only in reply to the board's communication. At such late stage of the proceedings, the objections could not be admitted into the proceedings. Moreover, the objections were based on documents that were prior art only in respect of claims not entitled to the first claimed priority date. Since the first priority date was validly claimed, all objections were moot.

X. The submissions of appellant II (opponent), insofar as they are relevant to the present decision, may be summarized as follows:

Main Request
Article 100(c) EPC; Article 123(2) EPC

The objection concerning the feature "*two promoters*", and in particular, whether there was a basis in the application as filed for the presence of two different promoters, was already discussed at first instance proceedings. There was no reason not to admit the objection into the appeal procedure.

The passages referred to by the patentee concerned specific embodiments that had no bearing for the claimed method. The disclosure on page 7, lines 2-3 was made in the context of a method of validating clones identified in a yeast two hybrid experiment (page 6, line 17). Page 6, lines 1-6 referred to a second construct for use with a first construct in a specific method of generating transgenic non-human organisms (page 5, line 12). Page 4, lines 1-4 referred to Figure 10 in which only one promoter was depicted. This was reflected in claims 5 (*in vitro* methods), 28 (method generating transgenic non-human organism) and 39 (*in vitro* method of validating clones) as originally filed, all of them directed to embodiments different from the feeding method of claim 73. Moreover, the wording "*one or more promoters*" in the application as filed was different from "*two promoters*"; the former could not be a formal basis for the latter.

A general teaching was found only on page 8, lines 9-16 of the application as filed and referred to a vector for use "*in each of the methods of the invention*". The vector was explicitly required to have two identical promoters. References throughout the application to just one ("*a*") transcription factor indicated that two identical promoters were used. The promoters were always mentioned in the context of binding one ("*a*") transcription factor and all examples were performed using two identical T7 promoters. There was no basis in the application as filed for two different promoters binding different transcription factors. The less so, since such embodiment would have resulted in technical problems (different transcription of sense and antisense DNA sequences) not addressed by the application as filed.

Article 100(b) EPC; Article 83 EPC
Admissibility of documents D15-D20 and D21-D25

Documents D15-D20 were filed to support arguments put forward under Article 83 EPC which the opposition division, in the decision under appeal, considered not to be substantiated by verifiable facts.

Sufficiency of disclosure

The teachings of the patent were exemplified by using a *C.elegans* (*nuc-1*) mutant. This mutant did not digest the DNA and therefore, allowed the DNA expression vector (introduced by feeding) to cross the gut wall. The teachings of the patent were not appropriate for all non-human animals. The patent failed to provide the technical information for a skilled person to carry out the invention over the whole breadth of the claim.

Documents D15-D20 showed that in complex organisms (non-human animals) feeding was not sufficient, since technical difficulties were encountered when performing the claimed method in several non-human animals. These documents described the presence of difficulties with dsRNA-expression *via* feeding bacteria in several non-human animals. Only specific non-human animals were suited for RNAi-silencing technology in combination with feeding. Besides the feeding problem, these documents showed examples of non-human animals which failed to show any RNAi-effect in general. For certain non-human animals, additional genes had necessarily to be expressed for a successful delivery of dsRNA in cells *via* bacteria, such as described in document D20 where the invasin (*Inv*) and the listeriolysin (*Hly*) genes were necessarily required. The patent however was silent on all these problems and on how to solve them.

According to the established case law, the disclosure of one way of putting the claimed invention into practice was enough for the purpose of Article 83 EPC only if thereby a skilled person could put the invention into practice over the whole scope of the claims. The post-published documents showed that this was not so in the present case.

Articles 87-89 EPC; Priority

The first priority document did not disclose any expression vector in which the two promoters were not identical. Claim 1 was thus not entitled to the first priority date.

Article 100(a) EPC; Articles 54 and 56 EPC

Since the first priority date could not be validly claimed, the method of claim 1 was anticipated by documents D4 and D5 (Article 54 EPC). Moreover, the combination of documents D4 and D12 or of documents D11 and D12 rendered the subject-matter of claim 1 obvious (Article 56 EPC).

XI. Appellant I (patentee) requested that the decision under appeal be set aside and the patent be maintained upon the basis of its Main Request, filed under cover of a letter dated 24 December 2014.

XII. Appellant II (opponent) requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Admissibility of the Main Request

1. In reply to the communication pursuant to Article 15(1) RPBA (cf. point V *supra*), appellant I withdrew all its requests then on file and made a former Auxiliary Request III, originally filed in reply to appellant II's statement of Grounds of Appeal (cf. point III *supra*), its Main Request.

2. The Main Request was a direct reply to appellant II's objections raised under Article 123(2) EPC and takes into account the board's comments made in its communication pursuant to Article 15(1) RPBA. No objections were raised by appellant II against its admissibility into the appeal proceedings and the board sees no reason for not admitting it.

3. Thus, the Main Request is admitted into the present appeal proceedings.

Main Request
Article 100(c) EPC; Article 123(2) EPC

4. In the opposition procedure no objection under Article 123(2) EPC was raised against Auxiliary Request II, finally upheld by the opposition division (cf. page 10, point 7 of the decision under appeal). However, an objection was raised in view of the then Auxiliary Request I. In the opponent's view, there was no basis in the application as filed for the two promoters of the expression vector in claim 1 not being identical (cf. page 7, point 5.1 of the decision under appeal). The objection was considered not to be relevant by the opposition division, which decided in patentee's favour (cf. page 7, point 5.2 of the decision under appeal).

5. In the statement of Grounds of Appeal, appellant II raised a single objection under Article 123(2) EPC against claim 1 of the Main Request (Auxiliary Request II in opposition procedure). With reference to three passages in the description of the application as filed, appellant II argued that there was no basis for an expression vector in which the DNA sequence was not required to be located between the two promoters (cf. page 7, point 2 of appellant II's statement of Grounds of Appeal). In the first of these three passages cited, the two promoters were explicitly described as being identical.

6. The board considered it as justified to address the issues raised under Article 123(2) EPC during the opposition proceedings of the present case, namely the nature (identical, non-identical) of the two promoters and their location in respect to the DNA sequence present in the expression vector (cf. pages 5 to 9, points 8 to 11 of the communication pursuant to Article 15(1) RPBA).

7. Since claim 1 of the Main Request has been amended with regard to Auxiliary Request II before the opposition division so as to require the DNA sequence to be located between the two promoters (cf. point VII *supra*), it remains to be assessed only whether there is a formal basis in the application as filed for the two promoters not being identical. In the board's view, this is indeed the case.

7.1 According to the application as filed, "*[i]n each aspect of the invention, the DNA library, DNA homologue or DNA fragment may be constructed in a suitable DNA vector*", wherein "*in one embodiment the DNA is located between two promoters on a vector capable of expressing*

dsRNA upon binding of an appropriate transcription factor to said promoters" (cf. page 3, lines 19-26 and page 4, lines 1-4). In the previous paragraph (cf. page 3, lines 10-18), it is stated that said DNA "*may, advantageously, be transfected or transformed into a microorganism, such as a bacterial or yeast cell, which may be fed to the organism*". None of these references requires the two promoters to be identical. The method of claim 1 for introducing dsRNA or DNA capable of producing dsRNA into a non-human animal by feeding as well as the elements or compounds used in said method, namely a bacterial or yeast cell comprising an expression vector as defined in claim 1, find thus a *verbatim* support in the application as filed.

7.2 In line with this general disclosure, the application as filed discloses the use of such DNA expression vector in several specific methods. One embodiment is a method using a first and second construct to generate a "*first and second transgenic organisms ... by transforming said first and second constructs into respective microorganisms for subsequent feeding to the respective organism*" (cf. page 5, lines 12-31). The second construct is characterized by the same technical features as the expression vector of claim 1 (cf. page 6, lines 1-6). Another example given is a method of validating clones identified in yeast two hybrid vector experiments (cf. page 6, line 17 to page 7, line 10). In none of these embodiments are the two promoters required to be identical.

7.3 Claim 73 as originally filed is directed to the same method as claim 1 of the Main Request, namely to "*[a] method of introducing dsRNA or DNA capable of producing dsRNA into an organism which method comprises feeding said organism with a suitable microorganism comprising*

an expression vector", wherein the vector is defined by back reference to the expression vector of claim 60 as originally filed. This expression vector comprises "*a promoter or promoters ... capable of initiating transcription of said DNA sequence to double stranded RNA upon binding of an appropriate transcription factor to said promoter or promoters*". There is no requirement for the promoters to be identical in any of these claims.

7.4 The board agrees with appellant I that technical considerations on the feasibility of the claimed method when using two non-identical promoters are not relevant for the examination of Article 123(2) EPC (cf. point IX *supra*). In any case, from a technical point of view, the application as filed always requires the two promoters to be "*capable of initiating transcription of said DNA sequence to double stranded RNA upon binding of* ***an*** *appropriate transcription factor to said promoter****s***" (emphasis added by the board). This requirement is reproduced *verbatim* in claim 1 of the Main Request.

8. In the light thereof, the Main Request fulfils the requirements of Article 123(2) EPC.

Articles 123(3) and 84 EPC

9. No objections were raised under these articles against Auxiliary Request II upheld by the opposition division (cf. page 10, point 7 of the decision under appeal) and none has been raised in appeal proceedings. There is no reason for the board to raise any on its own.

Article 100(b) EPC; Article 83 EPC

10. With its statement setting out the Grounds of Appeal, appellant II filed several post-published documents in order to support its arguments put forward under Article 83 EPC (cf. point II *supra*). In response also appellant I filed additional evidence (cf. point III *supra*). It is thus necessary to consider first whether this documentary evidence can be admitted into the appeal proceedings (Article 12(4) RPBA).

Admissibility of documents D15-D20 and D21-D25

10.1 In its communication pursuant to Article 15(1) RPBA, the board noted that the critical issue regarding the objection raised under Article 83 EPC had already been mentioned in the summons to oral proceedings issued by the opposition division (cf. page 4, point 6.2 of the board's communication and page 6, point 5.3.2 of the summons to oral proceedings issued by the opposition division on 7 July 2010). The opponent/appellant II, however, did not avail himself of the opportunity to submit new documentary evidence at that stage of the proceedings in order to support its arguments.

10.2 Nevertheless, in the present case, the following considerations have to be taken into account for the board to arrive at a decision:

- the new documentary evidence was filed by appellant II at the earliest stage of the appeal proceedings, namely with its statement of Grounds of Appeal;

- thereby, appellant I has had enough time in appeal proceedings to assess the relevance of the new documentary evidence and to provide counter-evidence, if so needed;

- indeed, this counter-evidence, namely documents D21-D25, has been filed and arguments based thereupon have been put forward by appellant I;

- it is acknowledged that the newly filed documentary evidence supports a critical issue and is therefore, in the same way as the newly filed counter-evidence, relevant for the board to reach a fair decision.

11. In view of these considerations, documents D15 to D20 and D21 to D25 are admitted into the appeal proceedings.

Sufficiency of disclosure

12. The teaching of the patent is not limited to a mere disclosure of the method of claim 1 in general, i.e. a method of introducing dsRNA or DNA capable of producing dsRNA into a non-human animal by feeding. The patent further provides explicit information directing the attention of a skilled person to several factors, parameters and conditions having a significant influence on the actual performance of this method.

12.1 The patent refers to the nature and properties of the dsRNA and of the bacteria or yeast cells transformed thereby. The importance of the stability of the dsRNA, arising both from the inherent properties of the dsRNA itself (specific nucleotide sequence, secondary structure and folding properties, such as presence and size of loops and stem-length, etc.) and from the particular environment and conditions within the bacteria or yeast cell, is made evident to a skilled person. In particular, the patent refers to the use of *E. coli* strains deleted in one or more RNAses other than the RNAseIII which is known to recognize specific

loops in the dsRNA and to enhance dsRNA formation (cf. page 8, lines 5-11 of the patent).

12.2 Another highly relevant piece of information given in the patent is that the performance of the feeding method depends on the ability of the dsRNA (within the transformed bacteria or yeast cell) to cross the gut wall of the non-human animal without being thereby destroyed or digested, i.e. the efficiency of dsRNA uptake and the stability of the dsRNA during said uptake. For this reason, the feeding method exemplified by the patent uses the *C. elegans* nuc-1 mutant, a preferred DNAse deficient *C. elegans* which allows the *E. coli* plasmid DNA, on which the worm feeds, to cross the gut wall without being destroyed (cf. page 10, lines 35-39 and page 11, paragraph [0057] of the patent). Post-published document D4 shows that *E. coli* expressing dsRNA confers specific interference effects on the nematode larvae of **wild-type** *C. elegans* feeding on said bacteria. These effects are shown to be dependent on the specific dsRNA expressed (*unc-22*, 85%; *fem-1*, 43%; GFP transgene, 12%).

12.3 In a different context the patent also refers to several other factors, which are part of the common general knowledge of a skilled person and which might have an influence on dsRNA uptake and digestion. Such factors are the stages of growth of the non-human animal (cf. page 8, lines 11-12 of the patent) and the actual components of the bacteria or yeast cell preparation on which the non-human animal feeds (cf. page 10, lines 53-55 of the patent). It is self-evident to a skilled person that "non-human animals" are limited to animals being sensitive to RNA interference (RNAi) (cf. page 7, line 17 of the patent).

12.4 Claim 1 is directed, only and exclusively, to a method of introducing dsRNA or DNA capable of producing dsRNA into a non-human animal by feeding. It does not require any particular degree or yield of dsRNA uptake and/or expression, let alone of inhibition of any specific target gene. Indeed, claim 1 does not even mention inhibition at all (cf. point VII *supra*).

13. Appellant II submitted post-published documents D15-D20 to demonstrate that the information provided by the patent was not sufficient to allow a skilled person to perform the claimed method over the whole scope of claim 1 (cf. point X *supra*). As counter-evidence, appellant I submitted post-published documents D21-D24 and prior art document D25 (cf. points II and III *supra*). A detailed examination of these documents is required for the board to arrive at a decision:

13.1 The mere reference in document D15 to unsuccessful "*preliminary experiments to introduce dsRNA into neonate larvae of S. litura ... by feeding through diet*" is not relevant, since the conditions under which these experiments were carried out are not disclosed (cf. page 46850, right-hand column, last paragraph). Document D15 does not define or characterize the diet used and, most relevant, does not state whether the insects were fed with bacterial or yeast cells comprising the dsRNA or whether they were fed with naked dsRNA.

Documents D21 and D22, filed as couter-evidence to document D15, report the successful inhibition of several target genes by ingestion of bacterially expressed dsRNA in two other *Spodoptera* species (*S. exigua* and *S. frugiperda*). These documents refer to factors which are also mentioned in the patent, such as

the stability of dsRNA and the relevance of the dsRNA nucleases (cf. page 6, left-hand column, lines 4-7 and 22-25 of document D22).

13.2 Document D16 reports the successful inhibition of the immunoresponsive midgut-expressed gene *TsetseEP* by feeding dsRNA to the tsetse fly *Glossina*. The document confirms the relevance of the information provided by the patent itself. First of all, the dsRNA delivery medium (bloodmeal) is defined and its importance explicitly acknowledged (cf. paragraph bridging pages 12 and 13 and page 15, right-hand column, lines 6-8). Reference is further made to several factors that might influence the stability and uptake of dsRNA (*inter alia*, species-specific intestinal conditions and stage growth; cf. page 15, right-hand column, last full paragraph) which are also identified in the patent (cf. point 12.3 *supra*). Although no inhibition is reported for a fat-body expressed transferrin gene (*2A192*), reasons for this failure are given. These are seen in the inability to distribute the RNAi signal due to the absence of the gene responsible for systemic spreading of the RNAi signal (cf. page 15, left-hand column, lines 6-38), rather than in a deficiency of the dsRNA feeding method (see also point 13.4 *infra*). Document D16 notes the usefulness of the dsRNA feeding method and the possible "*optimisation of dsRNA delivery in the meal*" with reference to the factors mentioned above (cf. page 16, left-hand column, last paragraph).

The possible optimization of the dsRNA feeding method and the limitations associated with RNAi are also mentioned in the patent itself, either in an explicit or implicit manner (cf. points 12.1-12.3 *supra*).

13.3 Documents D17 and D18 relate to protozoan parasites (*Leishmania* and *Trypanosoma cruzi*, respectively). The classification of protozoan parasites as non-human animals having the ability to be fed is contentious. Both parties have acknowledged that the content of these documents is not as relevant as the evidence provided by other post-published documents on file. It is thus not necessary to enter into a detailed analysis of these two documents.

13.4 Document D19 is a review article on RNAi in *Lepidoptera* and states that most of the negative results are anecdotal (see abstract). Several delivery methods are compared and reference is made to "*a great variation ... among different lepidopteran species with respect to their sensitivity to systemic RNAi*" (cf. page 234, right-hand column, lines 3-6). The document summarizes previous studies on dsRNA feeding (cf. page 237, left and right-hand columns) and refers to several factors that might be relevant for this delivery method, including the presence of (mid-gut) dsRNA degrading enzymes (cf. page 238, right-hand column, second paragraph and page 239, left-hand column, third paragraph). With regard to RNAi in general, reference is made to the identity and nature of the target gene and the stability and structural properties of the dsRNA used (cf. page 237, right-hand column, second paragraph, page 239, right-hand column, second paragraph to page 240, left-hand column, first paragraph).

Factors influencing the silencing effect and thus, the efficiency of RNAi in general, are also summarized in document D23 (cf. page 233, middle of the left-hand column to first paragraph right-hand column). This document was submitted as counter-evidence to document

D19 and reviews RNAi studies in insects with dsRNA being applied through different kinds of feeding (see Table 2).

As document D16, also documents D19 and D23 acknowledge the need for optimization of the dsRNA feeding method and the limitations associated with RNAi in general.

13.5 According to appellant II document D20 shows that the dsRNA feeding method for higher non-human animals requires several factors which are not mentioned in the patent. In particular, it relies on the presence of the invasin gene (*Inv*) and the listeriolysin O gene (*HlyA*) in the bacteria or yeast cell used. However, in the board's view, document D20 only confirms the information provided by the patent, namely that the bacteria or yeast cell comprising the dsRNA has to be able to cross the non-human gut wall, resulting in an efficient dsRNA uptake (cf. point 12.2 *supra*).

Indeed, document D24, filed as counter-evidence to document D20, shows that, for naturally invasive bacteria *Salmonella enterica* serovar *typhimurium* strain 7207, the *Inv* gene (whose function was already known in 1988; cf. document D25) is not necessary. Moreover, gene silencing is also measured in (*in vitro*) treated SW480 cells when the *HlyA* gene is not present (cf. paragraph bridging pages 96 and 97 of document D24).

14. The board concludes that none of the post-published documents D15-D20, filed by appellant II, casts serious doubts on the feasibility of the claimed method. In the light of the information provided by the patent, it lies within the normal technical abilities of a skilled person to set up the most appropriate, if not optimal,

conditions for carrying out an experimental assay for performing the method of claim 1 over its whole scope.

15. The requirements of Article 83 EPC are thus fulfilled.

Articles 87-89 EPC; Priority

16. The objection regarding the entitlement to the first claimed priority is based on the same facts and arguments discussed under Article 123(2) EPC (cf. point X *supra*). Since the specific paragraphs referred to by the parties are identical in both, the first priority document and the application as filed, the board sees no reason to diverge from the conclusion arrived at with regard to Article 123(2) EPC (cf. points 7 and 8 *supra*). Thus, the Main Request is entitled to the first claimed priority date.

Article 100(a) EPC; Articles 54 and 56 EPC

17. According to the decision under appeal, the opponent/ appellant II did not raise any objection under Articles 54 and 56 EPC against Auxiliary Request II before the opposition division (cf. page 11, points 10 and 11 of the decision under appeal). This auxiliary request, which was found to be allowable by the opposition division, is broader in scope than the present Main Request (cf. points I and VII *supra*). In its statement setting out the Grounds of Appeal, appellant II did not raise any objection under Articles 54 and 56 EPC but informed the board that it "*reserves the right to make further submissions*" (cf. page 8, point 3 of appellant II's Grounds of Appeal).

18. It was only in reply to appellant I's Grounds of Appeal that appellant II raised objections under Articles 54

and 56 EPC. The objection under Article 54 EPC was based on document D4 and reference was made to arguments put forward in opponent/appellant II's notice of opposition dated 29 September 2009. The objection under Article 56 EPC was based on a broad interpretation of the term "*feeding*" (not being limited to "*eating*") and with reference to ten different documents and to arguments put forward in said notice of opposition. However, these general arguments were not further elaborated (cf. page 2, point b) of appellant II's letter dated 7 September 2011).

19. None of these submissions are in line with the purpose of an appeal procedure as defined in the case law of the Boards of Appeal, where it is held that the appeal procedure is not a continuation of the opposition procedure but a distinct procedure in which any facts, evidence or arguments considered relevant must be resubmitted. A reference to the first-instance submissions cannot replace an explicit account of the legal and factual reasons for the appeal (cf. "Case Law of the Boards of Appeal of the EPO", 7th edition 2013, IV.E.2.6.3.b) and IV.E.2.6.4.a), pages 960 and 963, respectively).

20. In its reply to the board's communication pursuant to Article 15(1) RPBA, appellant II provided more detailed arguments under Articles 54 and 56 EPC (cf. pages 8 to 10, points 6 and 7 of appellant II's letter dated 26 November 2014). As regards Article 54 EPC, documents D4 and D5 were cited, document D5 being relevant only for a broad interpretation of the claims. As regards Article 56 EPC, two combinations of documents were mentioned, namely document D4 with D12 and document D11 with D12, document D11 being relevant only for a broad interpretation of the claims.

21. These arguments represent an amendment of appellant II's case and, according to Article 13(1) RPBA, they may be admitted and considered at the board's discretion. In the present case, the following issues are of relevance for the board to arrive at a decision:

21.1 Appellant II's arguments have been submitted at a late stage, indeed almost at the latest possible stage, of the appeal proceedings and thus, not in due time (Article 114(2) EPC).

21.2 The interpretation of the claims made by the opposition division, which was extensively discussed at the beginning of the decision under appeal (cf. page 2, point 2 of the decision under appeal), was not contested in appellant II's Grounds of Appeal. The issue concerning the date of public availability of document D12, which was disputed in opposition proceedings without a decision being taken (cf. page 3, point 3.1 of the decision under appeal), was not mentioned in appellant II's Grounds of Appeal or addressed at any time during appeal proceedings. The extremely late submission of arguments based on document D12 may render this issue relevant again.

21.3 Since the board has decided that the patent is entitled to the first priority date (cf. points 7 and 8 *supra*), documents D4 and D5 are not relevant prior art. Accordingly, there is no validly raised objection under Article 54 EPC. The first objection raised under Article 56 EPC is based on the combination of documents D4 and D12, which, in view of the board's decision on priority, cannot be validly raised. The second objection under Article 56 EPC is based on documents

D11 and D12 and relies on an interpretation of the claims which has not been addressed in appeal proceedings.

22. In view thereof, the board, exercising its discretion under Article 13(1) RPBA, does not admit appellant II's amendments to its case with regard to the issues of novelty (Article 54 EPC) and inventive step (Article 56 EPC) at this late stage of the appeal procedure (Article 114(2) EPC).

Adaptation of the description

23. At the oral proceedings, appellant I submitted amended pages 3, 4, 11 and 75 of the description to bring it in line with the main request. The board is satisfied that this has been done in agreement with the requirements of the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent as amended in the following version:

Description:

pages 5 - 10 and 12 - 74 of the patent specification as granted;

pages 3, 4, 11 and 75 of the amended patent specification as filed during the oral proceedings on 26 January 2015.

Claims:

claims 1 - 12 of the Main Request, filed under cover of a letter dated 24 December 2014.

Drawings:

Figures 1 - 19 of the patent as granted.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated