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DECISION of 12 January 2005

Case Number: T 0606/03 - 3.3.08
Application Number: 00974397.2
Publication Number: 1222262
IPC: C12N 15/10
Language of the proceedings: EN

Title of invention:
Conditional gene trapping construct for the disruption of genes

Applicants:
ARTEMIS Pharmaceuticals GmbH, et al

Opponent:
-

Headword:
Gene trap/ARTEMIS

Relevant legal provisions:
EPC Art. 53(a), 56
EPC R. 23d(d)

Keyword:
"- main and first auxiliary requests - exception to patentability - (yes)"
"- second auxiliary request - exception to patentability - (no)
- novelty and inventive step - (yes)"

Decisions cited:
T 0315/03, T 0019/90

Catchword:
-
Case Number: T 0606/03 - 3.3.08

DECISION
of the Technical Board of Appeal 3.3.08
of 12 January 2005

Appellants:
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Decision under appeal:
Decision of the Examining Division of the
European Patent Office posted 7 January 2003
refusing European application No. 00974397.2
pursuant to Article 97(1) EPC.

Composition of the Board:
Chairman: L. Galligani
Members: F. Davison-Brunel
          C. Rennie-Smith
Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse the European patent application No. 00 974 397.2 published as international application No. WO 01/29208 with the title "Conditional gene trapping construct for the disruption of genes".

The patent application was refused for lack of novelty of the subject-matter of claims 1, 2, 5, 6 and 10 to 17 then on file over the teachings of document (2). Furthermore, the examining division came to the conclusion that all claims lacked inventive step over the combination of the teachings of document (2) with any one of documents (1), (5) or (10). Finally, the remark was made that the subject-matter of claims 12 to 17 then on file was to be considered as an exception to patentability under Article 53(a) and Rule 23d EPC.

II. The applicants (appellants) filed an appeal, paid the appeal fee and submitted an amended set of claims together with the grounds of appeal.

III. The examining division did not rectify the contested decision and referred the appeal to the board of appeal (Article 109 EPC).

IV. The board sent a communication to convey its preliminary opinion regarding a number of issues which it would be useful to address before oral proceedings were summoned, inviting the appellants to file observations within a period of two months.
V. The appellants' observations were received in due time together with an amended set of claims.

VI. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal stating its preliminary, non-binding opinion as regards that amended set of claims.

VII. The appellants filed a reply in answer to this communication together with a new main request, an auxiliary request and seven new documents.

VIII. During oral proceedings which took place on 12 January 2006, the appellants filed a further (second) auxiliary request.

Claims 1, 7, 12 and 16 of the main request read as follows:

"1. A gene trapping construct capable of causing conditional mutations in genes, which comprises a gene disruption cassette comprising a polyadenylation site, inserted in a mutagenic or non-mutagenic manner, in sense or antisense direction relative to the gene to be trapped, said gene disruption cassette being flanked by two recombinase recognition sequences (RRSs) selected from mutant loxP sites, mutant frt sites and AttP/AttB sites, which are present in opposite orientation and which are specific to the site specific recombinases Cre, Flp, Φ C31-Int and λ-Int, said specific recombinases (i) being capable of unidirectional inversion of a double stranded gene disruption cassette being flanked by said two RRSs present in opposite orientation, and
(ii) producing the inverted double stranded gene disruption cassette in an amount of greater 75%, relative to the starting double stranded disruption cassette. (emphasis added by the board).

7. The construct according to any one of claims 1 to 3 which comprises
(a) a gene disruption cassette being oriented to be inserted in antisense orientation relative to the transcriptional orientation of the gene to be trapped and being flanked by two RRSs which are specific to a first site specific recombinase capable of unidirectional inversion of a double stranded gene disruption cassette, and
(a) a selection cassette, being positioned in sense direction relative to the transcriptional orientation of the gene to be trapped and being flanked by two RRSs of a second site specific recombinase in the same orientation.

12. A process for the generation of conditional mutations in a gene of a mouse comprising:
(i) installation of a gene trapping construct as defined in claims 1 to 9 in a suitable cell,
(ii) selection of cells in which the construct is incorporated in a gene,
(iii) identification and/or isolation of the gene in which the construct is incorporated,
(iv) deletion of the selection cassette from the trapped gene,
(v) induction of a mutation in the trapped gene by inversion of the gene disruption cassette.
16. A transgenic mouse obtainable by the method of claims 12 to 15."

Claims 2 to 6, 8 and 9 related to further features of the gene trapping construct of claims 1 and 7. Claims 10 and 11 were respectively directed to a cell comprising the gene trapping construct as defined in claims 1 to 9 and to the use of said cell for the identification and/or isolation of genes. Claims 13 to 15 related to further features of the process of claim 12. Claim 17 related to the use of the transgenic mouse according to claim 16.

The claims of the first auxiliary request essentially corresponded to the claims of the main request but claims 1 and 7 contained amendments which took into account an observation by the board under Article 84 EPC.

The second auxiliary request comprised 11 claims. Claims 1, 7 and 11 read as follows:

"1. A gene trapping construct capable of causing conditional mutations in genes, which comprises a gene disruption cassette comprising a polyadenylation site, said gene disruption cassette being flanked by two recombinase recognition sequences (RRSs) selected from mutant loxP sites, mutant frt sites and AttP/AttB sites, which are present in opposite orientation and which are specific to the site specific recombinases Cre, Flp, Φ C31-Int and λ-Int, said specific recombinases
(i) being capable of unidirectional inversion of a double stranded gene disruption cassette being flanked by said two RRSs present in opposite orientation, and (ii) producing the inverted double stranded gene disruption cassette in an amount of greater 75%, relative to the starting double stranded disruption cassette.

7. The construct according to any one of claims 1 to 3 which comprises
(a) a gene disruption cassette being flanked by two RRSs which are specific to a first site specific recombinase capable of unidirectional inversion of a double stranded gene disruption cassette, and
(a) a selection cassette, being positioned in opposite orientation relative to the gene disruption cassette and being flanked by two RRSs of a second site specific recombinase in the same orientation.

11. A transgenic mouse containing in an intron of a gene a gene trapping construct as defined in claims 1 to 9 in an antisense direction relative to the gene."

Claims 2 to 6 and 8 to 10 were identical to the corresponding claims of the main request. They were no claims corresponding to claims 11 to 15 and 17 of the main request.

IX. The following documents are mentioned in the present decision:

(2): WO 99/50426;


X. The appellants' submissions in writing and during oral proceedings insofar as relevant to the present decision are summarised as follows:

Main and first auxiliary requests; claim 16
Article 53(a) EPC, Rule 23d(d) EPC

The claimed transgenic mice carrying the gene trap construct of the invention in their genome were very potent tools for finding out the role of specific genes and ultimately developing pharmaceutical compounds to relieve any effects caused by misfunctioning of said genes. Evidence thereof was to be found in the many research developments which had taken place after the invention was made known to the public. As the transgenic mice were animal models which reflected what might happen in humans, they and their use were clearly of substantial medical benefit.
It could not be denied that the transgenic mice "in mutated form" would be likely to suffer, nor that their use in drug development might cause suffering. However, the transgenic mice as obtained by carrying out the invention were likely to suffer much less than transgenic mice - with a gene trap construct in their genome - as developed in the prior art. Indeed, because of the specific features of the gene trap construct, namely its ability to be inserted in the genome in two different orientations, one causing a mutation and the other not, the mice would mostly remain in a non-mutated state i.e. they would not suffer. It was only when they were manipulated for the purpose of substantial medical benefit that they might suffer.

For these reasons, the subject-matter of claim 16 did not fall under the prohibition of patentability under Article 53(a) and Rule 23d(d) EPC.

Second auxiliary request; claim 11

Article 123(2) EPC;
A basis for the subject-matter of this claim was found in the passage bridging pages 9 and 10 together with lines 1 and 2 on page 11.

Article 53(a); Rule 23(d) d EPC
The subject-matter of this claim had been restricted to transgenic mice which carried the gene trap in the intron of a gene in the non-mutagenic orientation. Thus, the mice did not suffer. The prohibition from patentability under Rule 23d(d) EPC did not apply.
Article 57 EPC

The claimed, non-mutated transgenic mice were of industrial applicability because of their unique genetic potential due to the presence of the gene trap construct in their genome. They could be manipulated in such a way as to produce animal models useful for the isolation of pharmaceutical products - for example, by crossing them with other mice expressing an enzyme capable of flipping the gene trap construct in the mutated orientation so that the resulting offspring was mutated.

Article 83 EPC

At the priority date, producing transgenic mice starting from genetically manipulated stem cells was done as a matter of routine as described on pages 1 to 3 of the application as well as in prior art documents (13) and (16).

Article 56 EPC, inventive step of the subject-matter of claim 1

The reasoning which led the examining division to a conclusion of lack of inventive step of the subject-matter of claim 1 was based on a combination of the teachings of document (2) with the teachings of documents relating to the specific integration or excision of any DNA into/from a given locus in a genome such as for example document (5) but also documents (1) or (10). Document (2) suggested a gene trap for creating conditional mutations comprising any recombinase recognition sequences (RRSs). The other
documents mostly related to the effects of specific RRSs on the efficiency of integration/excision events. None of said documents motivated the skilled artisan to use RRSs in a gene trap vector for conditional mutagenesis. In particular document (1) revealed an exchangeable trap system with two mutant, non-inverted RRSs flanking a reporter gene without a promoter with the aim of replacing the reporter gene by another. Comparing the teachings of document (1) with that of documents (5) or (10) made it clear that the latter references did not go beyond the teachings of document (1).

The skilled person, thus, had no reason to combine the teachings of document (2) and of these documents. Even if they were considered together, they still did not teach the key technical features of the invention - namely, mutated RRSs on each side of the gene trap and in reverse orientation, and the presence of a polyA termination site. Therefore, they did not make it obvious. To reach a conclusion of lack of inventive step on this basis could only be done with hindsight.

XI. The appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or first auxiliary request filed on 12 December 2005 or the second auxiliary request filed during the oral proceedings.
Reasons for the decision

Main request; claim 16
Article 53(a), Rule 23d(d) EPC

1. Claim 16 relates to a transgenic mouse, ie to a mouse the genetic identity of which has been modified. It must be assessed whether this subject-matter may be one for which European patents shall not be granted pursuant to Article 53(a) EPC. In accordance with the case law (T 315/03 of 6 July 2004, to be published in the OJ EPO), the first step in this assessment is to investigate whether Rule 23d(d) EPC applies, which states that:

"Under Article 53(a), European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the following:

(a)-(c)....
(d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes."

2. As the claimed transgenic mouse is obtainable by the process of claims 12 to 15, it has the gene trap construct of claims 1 to 9 inserted in its genome (see section VIII, supra). In claim 1, it is explicitly mentioned that the insertion may take place "in a mutagenic... manner, in sense... direction relative to the gene to be trapped". Thus, the scope of claim 16 extends, in particular, to a mouse for which the
modification in genetic identity results in a mutated phenotype. It is likely that in instances where the mutated gene is an essential one, the mutated mouse will suffer - a fact which was not challenged by the appellant.

3. On page 2 of the patent application, it is explained how conditional mutations - as are obtained with the present gene trap construct - are useful "to validate the utility of genes and their products as target for drug development". On page 3, it is stated that mouse mutants obtained with the gene trap technology "often develop a "loss of function phenotype" which sometimes will disclose the biological significance of a particular gene." (emphasis added by the board). It is clear from this statement that not all mutated mice will be of medical benefit, let alone of substantial medical benefit, because the benefit to be expected, namely serving as models for the development of pharmaceutical drugs - will more often than not depend on previous research having established the role of the targeted gene in a given pathology.

4. Taking together the findings in points 2 and 3 leads to the conclusion that claim 16 encompasses mice with a change in genetic identity for which no balance is struck between likely suffering and likely substantial medical benefit to man or animal. For this reason, the claimed subject-matter falls within the category of exceptions to patentability pursuant to Article 53(a) EPC of point (d) of Rule 23d EPC.
First auxiliary request; claim 16

Article 53(a) EPC; Rule 23d(d) EPC

5. Here again, the claimed transgenic mouse has the gene trap construct of claims 1 to 9 inserted in its genome. Claim 1 does not explicitly mention that the insertion may take place in a mutagenic manner, in a sense direction relative to the gene to be trapped. Yet, it is a matter of "chance" whether a given DNA (here, the gene trap construct) will insert into another DNA (here, the mouse genome) in one direction or the other. Thus, claim 16 encompasses mutated mice resulting from the insertion of the gene trap in the sense direction in the trapped gene. Consequently, the reasoning developed in relation to claim 16 of the main request applies equally to claim 16 of this request which thus also falls within the category of exceptions to patentability pursuant to Article 53(a) EPC of point (d) of Rule 23d EPC.

Main and first auxiliary requests; claims 11 to 15 and 17

6. At oral proceedings, further issues relating to claims 11 to 15 and 17 which had already been raised by the board in writing were also discussed: the clarity of claim 12, whether or not the process claims 12 to 15 were to be regarded as exceptions to patentability under Article 53(a) EPC, whether or not the use claims 11 and 17 complied with the requirements of Articles 57 or 83 EPC. Taking into account that:
   - it is enough that one claim is not allowable for an entire request to fail and that
   - claim 16 of the main and first auxiliary requests was found to be an exception to patentability
(see points 2 to 5 supra), an issue which it made sense to decide before entering any discussion on patentable matters,

the board sees no need to review here its findings in relation to these further points.

7. The main and first auxiliary claim requests are rejected as they contain subject-matter for which a European patent shall not be granted under Article 53(a) EPC and Rule 23(d) EPC.

Second auxiliary request

8. This claim request was filed at oral proceedings. It comprises 11 claims: claims 1, 7 and 11 are amended versions of claims 1, 7 and 16 of the main request (see section VIII, supra) while claims 11 to 15 and 17 of the main request are absent. The board understood these changes as having been made to take into account the tenets of the discussion which took place earlier in the oral proceedings and, therefore, agreed to consider the new claim request.

Articles 123(2) and 84 EPC

9. The subject-matter of claims 1, 7 and 11 finds a basis in the application as filed, on pages 8 and 9 (claim 1), on page 10, third paragraph (claim 7) and in the passage bridging pages 9 and 10 and page 11, lines 1 to 4 (claim 11).
10. The expression "inserted in a mutagenic or non-mutagenic manner, in sense or antisense direction relative to the gene to be trapped" found in claim 1 of the main request (see section VIII, supra) is absent from claim 1 of this request to take into account the board's objection that it introduced confusion insofar as these features were characteristics of the gene trap construct when inserted into the genome of an organism and not of the gene trap construct on its own as was being claimed. The equivalent expressions "being oriented to be inserted in antisense orientation relative to the transcriptional orientation of the gene to be trapped" and "being positioned in sense direction relative to the transcriptional orientation of the gene to be trapped" found in claim 7 of the main request are absent from claim 7 of this request for the same reason. In the board's judgment, these claims are now clearly worded. In claim 11, all technical features pertaining to the transgenic state of the claimed mouse are mentioned without any ambiguity.

11. The requirements of Articles 123(2) and 84 EPC are fulfilled.

Article 53(a) EPC; claim 11

12. As with claim 16 of the main request, it must be assessed whether the transgenic mouse of claim 11 constitutes subject-matter which falls within the category of exclusions of Rule 23d(d) EPC. On page 10 of the patent application, it is explicitly mentioned that the gene trap construct does not interfere with gene transcription "by residing on the non-transcribed DNA strand" i.e. when it is inserted in an intron in an
antisense direction relative to the gene which is trapped. In Figure 1 B., it is shown why the polyA is not recognized as a transcription termination signal in this specific configuration, how transcription thus goes on to the downstream exon in spite of the presence of the gene trap construct and how the intron containing said construct is eliminated from the RNA in the "usual manner" so that wild-type mRNA is formed. The mice which carry the gene trap construct in an intron in an antisense direction are, thus, not affected in their metabolism. At oral proceedings, this point was emphasized as being a key technical feature of the claimed invention with the fundamental consequence that the claimed mice did not suffer from the presence of the gene trap construct in their genome. Otherwise stated, the exploitation of the claimed invention, namely the production of the claimed transgenic mice, does not imply suffering. Accordingly, and unlike with the mice considered in T 315/03 (supra), the Rule 23d(d)-test which requires balancing likely animal suffering with likely substantial medical benefit does not apply in the present case.

13. It is true that mice which can be "derived" from these claimed mice by acquisition and expression of the recombinase gene will be mutated mice - the gene trap will have been flipped in the activated orientation - and that, as already observed in point 2 above, some of them at least are likely to suffer. However, these "subsequent" mice are not claimed and, therefore, do not fall within the invention and, thus, are outside the board's power of investigation.
14. In accordance with the case law (T 315/03 (supra)) a second test has to be applied when ascertaining whether or not transgenic animals are exceptions to patentability pursuant to Article 53(a) EPC, namely that which was enunciated in the decision T 19/90 (OJ EPO 1990, 476):

"The decision as to whether or not Article 53(a) EPC is a bar to patenting the present invention would seem to depend mainly on a careful weighing up of the suffering of animals and possible risks to the environment on the one hand, and the invention's usefulness to mankind on the other."

As is readily apparent from this wording, this test also is relevant in cases where the claimed transgenic animals are likely to suffer. For the same reasons as given in relation to the Rule 23d(d) test, it is not to be applied to the subject-matter of claim 11 as such.

15. Finally, it may be remembered that in T 315/03 (supra) which also deals with a case where transgenic mice are claimed which could serve as models for drug development (then against cancer), objections of economic, religious, moral or socio-cultural nature were presented against the patentability of animals in general as well as objections of an environmental nature such as that there might be a danger if the transgenic mice were to escape from the laboratory. These are issues which do not depend on whether or how the claimed animals have been manipulated and which, therefore, could equally arise in relation to the presently claimed transgenic mice. In the earlier decision, extensive reasons were given why they then
had no bearing on patentability (see sections 10 and 13 of the said decision). In the board's judgment, the present situation is no different in relation to these objections so that the same conclusion is warranted.

16. In view of these findings, the board concludes that the provisions of Article 53(a) EPC do not apply to claim 11 and that, therefore, the second auxiliary request may be assessed regarding the requirements for patentability.

**Articles 54, 83 and 57 EPC; all claims**

17. None of the documents on file disclose a gene trap construct characterised at the same time by:
   - the presence of **mutated** recombinase recognition sites
   and
   - the presence of said sites in **opposite orientation**
   and
   - the presence of a polyadenylation transcription termination signal.
The subject-matter of claims 1 to 11 is, thus, novel.

18. The patent application itself (see pages 8 to 10) provides evidence that the various DNA elements entering the composition of the claimed gene trap construct of claims 1 to 9 were available to the skilled person at the priority date as well as the DNA encoding the recombinase enzyme and selection markers. They could be assembled using conventional genetic engineering technology. The introduction of foreign DNA such as gene trap constructs in the mouse genome was
done as a matter of routine starting with embryonic stem cells as reflected on page 3, lines 16 to 33 of the patent application and also, for example, in documents (13) and (16) respectively published some seven and four years before the priority date. The requirements of Article 83 EPC are fulfilled.

19. The non-mutated transgenic mice have a unique genetic potential due to the presence of the gene trap in their genome. They can be used to produce animal models as targets for drug developments. Their industrial applicability is acknowledged.

Article 56 EPC; inventive step; all claims

20. The closest prior art is document (2) which describes a vector for introducing mutations in a genome which comprises two gene trap cassettes (see eg claim 1). The so-called 5' gene trap cassette contains DNA encoding a selection marker; its presence enables the identification of the cells which have integrated the vector in their genome. The so-called 3' gene trap cassette is the one intended to cause mutations in the trapped cellular genes, its essential elements are a promoter, a coding sequence (gene trap exon) and a splice donor site. Transcription starting from the gene trap promoter "runs through" the gene trap exon and the downstream introns/exons of the cellular gene. After splicing, a fusion mRNA is, thus, produced comprising the mRNA encoded by the gene trap exon linked to the mRNA encoded by the exons of the trapped cellular gene. The expression of said gene is, thus, altered and the cells with the gene trap vector integrated in their genome are expected to be mutated.
21. From page 9 to page 48 of document (2), considerations are also made on, in particular, possible features of individual DNA segments which may enter the composition of gene trap vector, as well as on methods of use and potential molecular genetic applications. Section 5.5.3 starting on page 42 discloses the concept of creating conditional mutations with gene trap vectors wherein the gene trap is comprised between two recombinase recognition sites in opposite orientation. This concept is illustrated by the following statement concerning a vector carrying a gene trap comprising the DNA encoding selective marker SAβgeo ending with polyA transcription stop signal (Fig.1) within two inverted sites (lox sites) recognized by the cre recombinase: "A retroviral vector containing SAβgeo flanked by inverted lox sites was integrated into an intron of the HPRT gene by homologous recombination. When SAβgeo was present in the forward orientation, HPRT function was abolished as demonstrated by survival of cells in the presence of 6-thioguanine. However, when cre recombinase was expressed in these cells, the orientation of SAβgeo was flipped to the reverse orientation and HPRT function was regained as demonstrated by growth of cells in HAT containing medium."

22. It must first be remarked that the invention document (2) is concerned with does not involve gene trap flipping or conditional mutagenesis (point 20 supra). Furthermore, as can be seen from the above quote extracted from the general considerations, document (2) does not in any way suggest that it might be desirable to elaborate further the gene trapping constructs for
conditional mutagenesis which it proposes. On the contrary, the impression is clearly given, that the gene trapping construct which is described solves the problem of inducing conditional mutagenesis in a satisfactory manner. Thus, starting from the teachings of document (2), it may already require inventive step to envisage that the concept of conditional mutagenesis via gene trapping could be refined.

23. Taking as an assumption that the skilled person would consider the - unrelated - teachings starting on page 43, line 18, of strategies for inducing conditional flipping by expressing the recombinase in a conditional manner, as evidence that different systems of conditional mutagenesis may be developed and, thus, somehow as an incentive to develop different gene traps, then the problem to be solved could be defined as elaborating a further gene trap construct for conditional mutagenesis.

24. The solution provided is a specific embodiment of the gene trapping construct described in point 21 supra, namely a gene trapping construct comprising a polyA termination signal between two recombinase recognition sites in inverted orientation with the further characteristics that the recombinase recognition sites on each side of the polyA transcription termination signal are mutated. This specific design was developed to take into account the fact that the recombinase recombines reversibly between identical recognition sites (such as two mutated sites) but that it is much less efficient at recombining between different recombinase recognition sites such as a wild-type site and a mutated site. Thus, where a mouse according to
the present invention - carrying the gene trap construct with its two mutated recombinase recognition sites in the genome in a non-mutated manner, in an antisense orientation - is crossed with a mouse which expresses the recombinase, the gene trap is flipped around to the mutating, sense orientation. In the process, a double-mutant recombinase recognition site is generated on the one side of the gene trap and a wild-type site is generated on the other side. This configuration is not recognised or only poorly recognised by the recombinase with the important consequence that the mutated state is stable.

25. In contrast, as no specific measures are taught in document (2) for ensuring that the recombinase does not go on flipping the gene trap construct from the mutating to the non-mutating orientation and vice versa, it cannot be expected that the mutated state would be distinguishable from the non-mutated state in a reliable and stable manner. The claimed gene trap is, thus, clearly advantageous over the gene trap mentioned in the closest prior art.

26. At first instance, it was concluded that the subject-matter of claim 1 lacked inventive step when combining the teachings of document (2) with those of either of a number of documents (documents (1), (5) or (10)). Document (10) is concerned with the site specific integration of DNA into wild-type or mutant recombinase recognition sites introduced in the plant genome. Document (1) is concerned with replacing the reporter gene of a trap vector already inserted in the genome of embryonic stem cells with another reporter gene by an integration/excision mechanism. Document (5) is a
research study on the frequency of targeted over random integration in the genome of embryonic stem cells, of vectors comprising the neo marker gene between mutated or non-mutated recombinase recognition sites. The last paragraph in this document reads: "The advantage of this mutant lox system is that only a mutant lox site is needed as the chromosomal target. We believe that the method described here will be useful for genetic manipulation in ES cells, including conditional gene targeting and gene trapping, as this system allows site specific integration of any DNA sequence into a defined lox site." What is meant by this statement is not explained further but it can only be remarked that gene trap flipping is not a part of the system which is described in document (5). In conclusion, what may be said of these three documents is that, while the science which they describe relies to some extent on the same observation as the present invention does, namely a difference in efficiency of the recombinase depending on the nature of the recognition sites, they are not concerned with gene trap flipping as a means for introducing conditional mutations into a genome.

27. In the board's judgment, combining the teachings of a document (document (2)), which hardly provides any incentive to formulate the problem solved by the invention, with the teachings of documents (documents (1), (5) or (10)), which are not concerned with the same problem while admittedly relying on the same scientific observation for their own purposes, cannot lead to a conclusion of lack of inventive step without exercising hindsight.
28. For the reasons given in points 20 to 27, the board concludes that the claimed subject-matter fulfils the requirements of Article 56 EPC.

29. In summary, the second auxiliary claim request does not contain subject-matter in respect of which European patents may not be granted pursuant to Article 53(a) and Rule 23(d) EPC, and the claimed subject-matter fulfils the requirements for patentability.

Order:

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of the second auxiliary request filed during the oral proceedings and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski L. Galligani
Case Number: T 0606/03 - 3.3.08

DE C I S I O N
of 10 March 2006
correcting errors in the decision of the appeal case T 0606/03
of the Technical Board of Appeal 3.3.08
of 12 January 2005

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Decision under appeal:
Decision of the Examining Division of the
European Patent Office posted 7 January 2003
refusing European application No. 00974397.2
pursuant to Article 97(1) EPC.

Composition of the Board:
Chairman: L. Galligani
Members: F. Davison-Brunel
C. Rennie-Smith
In application of Rule 89 EPC, the decision in the appeal case T 606/03 is corrected in that the date on which the decision was given is the 12 January 2006 (underlined the correction), cf. Annex.

The Registrar:      The Chairman:

A. Wolinski       L. Galligani