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D E C I S I O N
of 22 September 2003

Case Number: T 0748/00 - 3.3.8

Application Number: 92920422.0

Publication Number: 0604552

IPC: C07H 21/00

Language of the proceedings: EN

Title of invention:
Method of synthesizing diverse collections of oligomers

Patentee:
AFFYMAX TECHNOLOGIES N.V.

Opponent:
Pharmacopeia, Inc.

Headword:
Oligomer libraries/AFFYMAX

Relevant legal provisions:
EPC Art. 123(2), 83, 54, 56
EPC R. 57a

Keyword:
"Main request and first auxiliary requests - added subject-matter - yes"
"Second auxiliary request - sufficiency of disclosure - yes"
"Second auxiliary request - novelty and inventive step - yes"

Decisions cited:
T 0113/86, T 0505/00

Catchword:
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Case Number: T 0748/00 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 22 September 2003

Appellant: (Proprietor of the patent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 11 April 2000 revoking European patent No. 0604552 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 604 552 with the title "Method of synthesizing diverse collections of oligomers" was granted with 15 claims based on the International application WO 93/06121 filed as PCT/US92/07815.

Independent claims 1, 2, 9 and 12 as granted read as follows:

"1. The use of identifier tags to enable subsequent identification of reactions through which members of a library of different synthetic compounds have been synthesised in a component by component fashion and consequent deductive structural identification of said members."

"2. A library of different synthetic compounds, which compounds are obtainable by synthesis in a component by component fashion which links each compound to one or more identifier tags which enable subsequent identification of reactions through which said components were incorporated and consequent deductive structural identification of said members."

"9. A tagged synthetic oligomer library produced by synthesizing on each of a plurality of solid supports a single oligomer sequence and one or more identifier tags identifying said oligomer sequence, said oligomer sequence and identifier tags synthesized in a process comprising the steps of:

(a) apportioning said supports among a plurality of reaction vessels;

(b) exposing said supports in each reaction vessel to a first oligomer monomer and to a first identifier tag;

(c) pooling said supports;

(d) apportioning said supports among a plurality of reaction vessels;

(e) exposing said supports to a second oligomer monomer and to a second identifier tag; and

(f) repeating steps **(a) through (e) from at least one to twenty times**." (emphasis added by the Board)

"12. A method of recording each step in a sequence of oligomer monomer additions in the synthesis of an oligomer library, the method comprising adding an identifier tag in conjunction with the addition of each monomer, and performing at least two cycles of monomer and tag addition, thereby forming a series of identifier tags identifying said oligomer sequence."

As for the remaining claims: dependent claims 3 to 8 were directed to embodiments of claim 2; independent claim 10 was directed to a method of preparing a tagged synthetic oligomer library; independent claim 11 was concerned with a solid support; dependent claims 13 and 14 were embodiments of claim 12 and independent claim 15 was directed to an oligomer library obtainable by a process of claims 12 to 14.

II. An opposition was filed requesting revocation of the patent on grounds of lack of novelty, lack of inventive step and lack of sufficient disclosure. During opposition proceedings, the Patentees filed new claims of a main request and of auxiliary requests 1 to 4.

By a decision within the meaning of Article 102(1) EPC dated 11 April 2000, the Opposition Division revoked the patent. It was decided that the main request and auxiliary requests 1 and 2 then on file failed to fulfil the requirements of Articles 84 and/or of Article 123(2) EPC and of Rule 57a EPC. Sufficiency of disclosure was found lacking with regard to the invention as claimed in the auxiliary requests 3 and 4 (Article 83 EPC), since the invention could not be carried out over the whole scope of the claim.

III. The Appellants (Patentees) lodged an appeal against the decision of the Opposition Division, paid the appeal fee and filed a statement of grounds of appeal together with a **new main request** and **new first and second auxiliary requests**.

Independent claims 1 and 4 of the **main request** (claims 1 to 5) read as follows:

"1. A method of recording each step in a sequence of oligomer monomer additions in the synthesis of an oligomer library, the method comprising synthesizing each oligomer on a solid support and at a separate location adding on said support a chemically compatible identifier tag in conjunction with the addition of each monomer, and performing at least two cycles of monomer

and tag addition, thereby forming a series of identifier tags identifying said oligomer sequence."

"4. A tagged synthetic oligomer library produced by synthesizing on each of a plurality of solid supports a single oligomer sequence and, at a separate location on said support, one or more identifier tags identifying said oligomer sequence, said oligomer sequence and identifier tags synthesized in a process comprising the steps of:

(a) apportioning said supports among a plurality of reaction vessels;

(b) exposing said supports in each reaction vessel to a first oligomer monomer and to a first identifier tag;

(c) pooling said supports;

(d) apportioning said supports among a plurality of reaction vessels;

(e) exposing said supports to a second oligomer monomer and to a second identifier tag; and

(f) repeating ***steps (c) through (e) from at least one to forty times***." (emphasis added by the Board)

Claims 2 and 3 related to further features of the method of claim 1. Claim 5 related to a method for preparing a tagged synthetic oligomer library including essentially the same steps as in the method in claim 4.

Claims 1 and 4 of the **first auxiliary request** (claims 1 to 5) differed from claims 1 and 4 of the main request respectively in that:

- in claim 1 the feature "performing at least two cycles of monomer and tag addition, thereby forming a series of identifier tags identifying said oligomer sequence" was replaced by the feature "performing **from two to five cycles** of monomer and tag addition, thereby forming a series of identifier tags identifying said oligomer sequence." (emphasis added by the Board);

- in claim 4, feature (f) read "repeating steps (c) through (e) from **one to three times"** (emphasis added by the Board).

Claims 1 and 4 of the **second auxiliary request** (claims 1 to 5) differed from claims 1 and 4 of the main request respectively in that:

- in claim 1, the feature "and performing at least two cycles of monomer and tag addition, thereby forming a series of identifier tags identifying said oligomer sequence" was replaced by the feature "and performing **two or three cycles** of monomer and tag addition, thereby forming a series of identifier tags identifying said oligomer sequence." (emphasis added by the Board);

- in claim 4, feature (f) read "repeating steps (c) through (e) **once**" (emphasis added by the Board).

IV. The Respondents (Opponents) withdrew their opposition on 9 January 2001.

V. The Board sent a communication pursuant to Article 11(2) of the Rules of Procedure of the Boards of appeal together with the summons to oral proceedings, indicating its preliminary, non-binding opinion. In particular, the necessity of discussing whether or not the amendment in claim 4 of the main request was occasioned by grounds of opposition was emphasized (cf. point 2 of the communication). Furthermore, it was mentioned that claim 4 could be held to fail to fulfil the requirements of Article 123(2) EPC since it related *inter alia* to a tagged synthetic oligomer library where the longest oligonucleotide comprised 41 monomeric units, which library did not seem to have been disclosed in the application as filed (cf. point 4 of the communication). It was also pointed out that the application as filed did not seem to disclose two to five cycles or two to three cycles of monomer addition in relation to tagged oligomers, which, therefore, raised doubts as to whether the subject-matter of claim 1 of the first and second auxiliary requests fulfilled the requirements of Article 123(2) EPC (cf. point 7 of the communication).

VI. The Appellants informed the Board that they would not be attending the oral proceedings and that they did not maintain their request for oral proceedings. These were cancelled. No substantive reply to the Board's provisional view nor amended claim requests were filed.

VII. The following documents are referred to in the present decision:

(4): Smith, L.M. et al., Nature, Volume 321, 1986, pages 674 to 679;

(5): Furka, A. et al., Int.J.Peptide Protein Res. Volume 37, 1991, pages 487 to 493;

(7): Cwirla, S.E. et al., Proc.Natl.Acad.Sci.USA, Volume 87, August 1990, pages 6378 to 6382;

(13): WO 90/14441;

(47): Declaration of Professor M. Bradley dated 30 October 1999 and accompanying attachments;

(53): Declaration of Professor A. Furka dated 24 July 2000 and accompanying attachments;

(54): Second declaration of Professor M. Bradley dated 16 August 2000 and accompanying attachments.

VIII. The Appellants' arguments in writing insofar as they are relevant to the present decision may be summarized as follows:

Main request; claim 4

Rule 57a EPC

The amendment carried out in claim 4, which corresponded to claim 9 as granted was aimed at correcting a drafting error in the claim which existed

from the very beginning. It was allowable since it disposed of an inconsistency between the claim and the description. In accordance with the case law (cf. eg. T 113/86 of 28 October 1987), correcting the error did not constitute an abuse of the opposition proceedings. The claims being considerably limited vis-à-vis granted claims 1 and 2, it was necessary to maintain at least some reasonable coverage for the general principle of the invention, ie the combinatorial "split and pool" synthesis format which was not limited to even-numbered oligomeric units only, but included also the odd-numbered ones.

Article 123(2)EPC

The subject-matter of claim 4 at issue comprised libraries containing tagged oligomers with an even or an odd number of monomers. It was not denied that the corresponding granted claim 9 (which corresponded to claim 14 as filed) related to tagged oligomers with only an even number of oligomeric units, in consequence of the repetition of a two-unit cycle. However, it was wrong to base an Article 123(2) EPC objection entirely on the wording of just one claim. There was ample basis in the application as filed for the application of the combinatorial "split and pool" synthesis format to both even and odd numbered oligomeric units. For example, claim 21 as filed clearly related to a process for making libraries comprising oligomers with an even or odd number of monomers. The same information could also be found in the application as filed on page 3, line 35 onwards, page 12, lines 14 to 16, page 13, line 25 onwards and example 3G. Libraries comprising oligomers with an even or odd number of monomers were, thus, part

of the original disclosure. The requirements of Article 123(2) EPC were fulfilled.

First and second auxiliary requests

Article 123(2) EPC

The first auxiliary request was limited to "dimeric" to pentameric" library members. Basis for the limitation of claim 1 to no more than five cycles of monomer and tag addition could be found in a number of places in the application as filed. Page 7 line 34 of the B specification referred to oligomers usually being "from 3 to 8 residues in length". This implicitly included tagged pentameric material. Pentapeptides were specifically disclosed eg in Examples 1 and 2. Tagged tetrameric materials were clearly within the scope of granted claims 12 and 14. Tetramers were also implicitly disclosed in the expression "from 3 to 8 residues in length". Tagged trimeric and dimeric materials were mentioned on page 7, line 12 and on page 5, line 21, respectively. Thus, each of the individual possible oligomer sizes embraced by the first auxiliary request were explicitly disclosed. As the second auxiliary request limited the situation further referring only to "dimeric" or "trimeric" structures there could be no Article 123 problem for either claim requests.

IX. The Appellants requested that the patent be maintained on the basis of the main or first or second auxiliary requests submitted together with the grounds of appeal. Alternatively, if the Board was negatively minded about the issues of novelty and inventive step, they

requested referral to the Opposition Division for the issues to be considered by the first instance prior to any review at appellate level.

Reasons for the Decision

Main request

Rule 57a EPC, Article 123(2) EPC; claim 4

1. When compared with claim 9 as granted (which is identical to claim 14 of the application as filed), claim 4 of the main request now under consideration carries, in addition to the introduction of the feature "at a separate location on said support", an amendment in the process step (f) which comprises two distinct parts. Firstly, the steps to be repeated are the steps **(c) through (e)** rather than the steps (a) through (e), and, secondly, the number of times these steps can be repeated is said to be **"from at least one to about forty times"** rather than "from at least one to about twenty times".

2. The Opposition Division indicated in their decision that the amendment in the then corresponding claim was not occasioned by grounds of opposition (cf. page 7, third paragraph of the reasons). The Appellants argued that the change in the steps to be repeated was allowable as it was done in order to correct an obvious mistake: repeating steps (a) to (e) from one to about twenty times as earlier claimed led to the non-sensical conclusion that the claimed process was meant only to allow the synthesis of oligonucleotides with an even

number of monomers. To back up their position, they cited the decision T 113/86 (see *supra*) where it was found that "*voluntary amendments...which are not necessitated by any of the grounds of opposition... should in principle not be allowed...However,...the removal of an inconsistency between a claim and the description should be allowed if the inconsistency arises from an error...*"

3. The Board agrees that the general teaching in the patent in suit is that of tagged oligomers with an odd or even number of monomers. Indeed, the patent specification discloses tagged oligomers with an odd or even number of monomers on page 8, lines 36 to 44. A method for obtaining tagged pentamers is described in Example I. In Example III, the parallel synthesis of peptides and oligonucleotide tags on carboxyl beads is described. It is stated in point G: "The methods of procedures (e) to (f) are then repeated...until the desired peptide and the oligonucleotide coding region are completely assembled.". Claim 12 as granted which is identical to claim 21 as originally filed is also directed to a method for synthesizing tagged libraries which comprise oligomers with an even or odd number of monomers. Thus, in principle, the change of "(**a) to (e)**" to "**(c) to (e)**" can be seen as an allowable amendment removing an inconsistency.

4. Nonetheless, as mentioned above, there is a second part to the amendment which concerns the number of times the steps can be repeated. In the Board's judgment, this part of the amendment does not amount to the correction of a mistake which would be immediately obvious from reading the patent specification since the

specification consistently refers to repetitions of steps "from at least one to twenty times".

5. In the grounds of appeal, the Appellants did not provide any arguments as to why the amendment as a whole should be considered as occasioned by grounds of opposition. They decided to make no submissions in this respect even after the Board indicated in its communication that the issue arising from Rule 57a EPC should be discussed at oral proceedings. This occurred although they expressed their intention not to take part in the proceedings and even withdrew the request for oral proceedings, thereby implicitly admitting that they accepted a decision by the board on the state of the file.

6. The only explanation given for the second part of the amendment in question is found in the submissions made before the Opposition Division with letter dated 2 November 1999 (see page 9 thereof) where it is stated: "Amended step (f) also specifies that the repeat steps must be carried out up to forty times **(to achieve the same upper limit for synthesis covered by the original claim 9 as granted.)**" (emphasis added by the Board).

7. The latter explanation, however, contradicts the stated purpose of the amendment which allegedly was merely to correct a drafting error which was there from the beginning (ie indicating steps (a) to (e) instead of (c) to (a): cf. first part of the amendment) because the second part of the amendment (ie change "from at least one to twenty times" into "from at least one to forty times") takes advantage of the upper limit created by and having a basis only in the alleged error. Such a

partial correction cannot be justified under Rule 88 EPC. Further, this voluntary amendment creates an inconsistency with the description. Nowhere in the application as filed can the expression "from at least one to forty times" be found, either explicitly or implicitly, the emphasis being - as already stated - on repeating the steps "from at least one to twenty times". As a matter of fact, claim 4 now covers with the figure "forty times" a process which leads to the production of a specific tagged synthetic oligomer library comprising oligonucleotides with the length of 42 units, which library is not disclosed in the application as filed. This also constitutes an offence against Article 123(2) EPC.

8. Thus, in the Board's judgement, the introduction in claim 4 of the feature of a number of repetitions "from at least one to forty times" cannot be seen as an answer to any ground of opposition (Rule 57a EPC) or as an amendment removing an inconsistency under Rule 88 EPC (cf. decision T 113/86, *supra*), and is, moreover, contrary to the requirements of Article 123(2) EPC. Consequently the main request is rejected.

First auxiliary request

9. In comparison with claim 12 as granted (identical to claim 21 as filed), claim 1 of this request requires (i) synthesizing each oligomer **on a solid support**; (ii) adding the tag **at a separate location** of said support; (iii) that the tag be **chemically compatible;** (iv) that **two to five cycles** of monomer and tag addition be performed.

10. Basis for features (i) to (iii) is found in the application as filed which indicates how the tagged oligomer libraries can be constructed on solid supports like beads or particles, the identifying tags being attached either to the oligomer or to the solid support to which the oligomer is attached (thus, a separate location) (cf. eg. passage bridging pages 15 and 16). The use of compatible chemistries is a self-evident requirement of the whole exercise (cf. eg. page 17, line 7).

11. As regards feature (iv), the application as filed contains no *expressis verbis* disclosure of the process of claim 1 with an upper limitation to five cycles of monomer and tag addition. The Appellants essentially argued that a basis for the claimed method could be found in the disclosure of oligomers comprising from two to five residues.

12. The Board is not convinced by this argument because the number of cycles to be accomplished to obtain an oligomer comprising from 2 to 5 residues does not necessarily equate with the number of residues fixed on the support. This is evident from Example I where a tagged pentamer is obtained by performing two cycles of monomer addition, the first monomer comprising four residues. Indeed, the application as filed defines "monomers" as "any member of the set of molecules which can be joined together to form an oligomer or polymer" (cf. page 8, lines 10 to 17), the term not being limited to molecules consisting of only one residue (cf. eg. dimers).

13. Auxiliary request 1 cannot be allowed as claim 1 does not fulfil the requirements of Article 123(2) EPC.

Second auxiliary request

Rule 57a EPC

14. In comparison with granted claim 12 (identical to claim 21 as filed) and granted claim 2 (based on claim 1 as filed), claims 1 and 4 of this request require (i) synthesizing each oligomer **on a solid support**; (ii) adding the tag **at a separate location** of said support; (iii) that the tag be **chemically compatible;** (iv) that **two or three cycles** of monomer and tag addition be performed (claim 1) or that three cycles of monomer and tag addition be performed (claim 4). The claims were so worded to avoid objections of lack of sufficient disclosure likely to be raised in relation to claims of broader scope. They are permissible under Rule 57a EPC.

Article 123(2)(3) EPC

15. Claim 1 of this request differs from claim 1 of the first auxiliary request only in respect of feature (iv). As already mentioned in relation to the first auxiliary request, features (i) to (iii) are fairly based in the application as filed. As regards feature (iv), it is noted that claim 21 as filed which was identical to claim 12 as granted (cf. Section I above) required "at least two cycles" to be performed. Furthermore, the application as filed refers explicitly to a 3-step synthesis for tagged libraries (cf. eg. page 19, lines 16 to 28 with reference to Figure 2). Thus, the

claimed method comprising two or three cycles of monomer and tag addition can be directly and unambiguously derived from the application as filed. In the context of said application, features (i) to (iv) as a whole are disclosed because it is manifest that conditions (i) to (iii) apply generally to all embodiments described therein, ie also in relation to those characterized by feature (iv). Thus, in the Board's judgment, claim 1 of this request satisfies the requirement of Article 123(2) EPC.

16. The same holds true for the remaining claims, in particular for independent claim 4 where feature (f) has been amended to read "repeating steps c) through e) once" which amounts to performing three cycles of monomer and tag addition, this being - as stated - supported by the original disclosure.

17. The scope of protection of the claims of this request is restricted in comparison with that of the claims as granted. Thus, the requirements of Article 123(3) EPC are met.

Article 83 EPC

18. Claim 1 relates to a method for recording each step in the synthesis of an oligomer library, which method includes any kind of oligomers: nucleic acids, polysaccharides, peptides etc..., as well as any kind of identifier tags: oligonucleotides, magnetic or electronic encoded information, fluorescent tags.

19. In the patent specification, pages 8 and 9, a generic method is described for producing a peptide oligomer

library tagged with oligonucleotides. The parallel synthesis of peptides and oligonucleotide tags on carboxyl beads is reported. Examples are also provided of pentapeptides which are fluorescently tagged.

20. In their decision, the Opposition Division found this disclosure insufficient for the reasons, in particular, that:

- the field to select the tags from was far too wide,

- oligonucleotides could not always be used as tags and alternative tags, especially peptides, were not sufficiently disclosed.

- fluorophore tagging had not been proven to be an alternative to oligonucleotide tagging.

No written evidence was cited in support of these objections. Nor are there any experimental data on file to support them. In the Board's judgment, they do not amount to more than mere assumptions which, as already established in the case law (see for example, T 505/00 of 25 March 2003) do not meet the standard required to prove that the requirement of Article 83 EPC is not fulfilled.

21. A number of expert opinions were filed by the Appellants. In document (53), it is said that the teachings of the patent would leave the scientist in an excellent position to put the disclosed principle into practice using the diversity of chemistries available in 1991. A table is provided in document (54) of the

known chemistries likely to be used for the formation of oligomers in relation to compatibility with some of the potential tagging methodologies described in the patent in suit (radioactive tags, fluorophores, peptides, N-alkylated peptides). In document (47), it is stated that the scientist of ordinary chemical knowledge in 1991 would have readily understood from the patent specification that peptides may be a source of tags and would have known how to reduce the labile nature of the peptidic bonds. Peptides/modified peptides are mentioned as capable of providing tags for "comfortably over 90% of potential library chemistries".

22. In view of these statements and in the absence of any evidence on file to the contrary, sufficiency of disclosure is acknowledged.

Article 54 EPC

23. There are no documents on file disclosing methods for making tagged libraries whereby the oligomers are synthesized on a solid support and the identifier tag is **located at a separate location on said support**. The subject-matter of claims 1 to 5 is, thus, novel.

Article 56 EPC

24. The closest prior art is document (5) which discloses the solid phase synthesis of mixture of peptides with predetermined sequences (passage bridging pages 487 and 488). The method comprises the steps of:

- apportioning the solid support (resin) among a plurality of vessels,

- exposing each of the supports to the desired amino acid,

- mixing the supports so obtained,

- repeating the last two steps until the peptides of the desired length and sequences are formed.

The identification of the sequence in amino-acids of any of the peptides thus obtained is done (1) by separation by HPLC followed by sequential degradation or (2) by computer-associated paper electrophoretic identification (page 489, right-hand column). It is stated on page 493: *"...determination of the complexity of the mixtures ...needs further investigation."*

25. Starting from the closest prior art, the problem to be solved can be defined as developing a method for an easier identification of the sequences of specific peptides in a mixture.

26. The solution provided is to add identifier tags on the solid support in parallel to the oligomer (eg. peptide) synthesis, each identifier tag being characteristic of the nature and position of a specific monomer (eg. amino acid) in the oligomer. The Board is satisfied that this method solves the above mentioned problem.

27. There is no document on file which, when combined with document (5), suggests the use of a binary system such as this. The peptides present in the library obtained by biological means described in document (7) are

identified by the DNA sequences encoding them. Thus, document (7) does not suggest setting up a system of identification in parallel to the synthesis of the oligomer (peptide) library. In document (13), the attachment of nucleic acid tags to substances such as explosives, pollutants, paper goods and pharmaceutical products is described. The tagging is not carried out to monitor the steps of synthesis of the substance to be tagged. Thus, the document is no more relevant than any of the other documents on file such as, for example, document (4) which discloses fluorescence as a means to identify individual nucleotides present in a pre-existing DNA fragment while sequencing it.

28. Inventive step is, thus, acknowledged.

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 maintain the patent on the basis of the second auxiliary request filed with the statement of grounds of appeal and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski L. Galligani