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Datasheet for the decision
of 20 June 2018

Case Number: T 0637/13 - 3.3.01
Application Number: 01902520.4
Publication Number: 1203238
IPC: G01N33/543, G01N33/68, B01J19/00, C07K1/00
Language of the proceedings: EN

Title of invention:
METHODS OF GENERATING PROTEIN EXPRESSION ARRAYS AND THE USE THEREOF IN RAPID SCREENING

Patent Proprietor:
Sengenics Corporation Pte Ltd

Opponent:
Protagen AG

Headword:
Protein arrays/SENGENICS

Relevant legal provisions:
EPC Art. 123(2)
RPBA Art. 12(4), 15(3)
EPC R. 115(2)
Keyword:
Amendments - added subject-matter (yes)
Late-filed requests - admitted (yes)
Oral proceedings - held in absence of the parties

Decisions cited:
G 0002/10

Catchword:
Case Number: T 0637/13 - 3.3.01

DECISION
of Technical Board of Appeal 3.3.01
of 20 June 2018

Appellant: Protagen AG
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Decision under appeal: Decision of the Opposition Division of the European Patent Office posted on 12 December 2012 rejecting the opposition filed against European patent No. 1203238 pursuant to Article 101(2) EPC

Composition of the Board:
Chairman A. Lindner
Members: T. Sommerfeld
M. Blasi
Summary of Facts and Submissions

I. European patent No. 1 203 238 entitled "Methods of generating protein expression arrays and the use thereof in rapid screening" was granted with 11 claims. The patent is based on European patent application No. 01902520.4, which had been filed as an international application published as WO 2001/057198.

Independent claim 1 as granted read as follows:

"1. A method of generating a protein array which comprises
(a) providing a plurality of cDNA molecules encoding proteins which are each tagged at either the N- or the C-terminus with a marker moiety;
(b) expressing the individual tagged proteins in a spatially separated format;
(c) purifying and immobilizing each tagged protein in a spatially defined format to produce a protein array on a solid support, whereby specific interactions between the tag and the solid support are used in both said purifying and immobilizing."

II. Notice of opposition was filed, the opponent requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Articles 54(2) and 56 EPC and Article 100(a) EPC) and added subject-matter (Article 100(c) EPC).

III. By its decision announced at oral proceedings, the opposition division rejected the opposition under Article 101(2) EPC.

IV. The opponent (appellant) lodged an appeal against that decision. With its statement of grounds of appeal it
requested that the opposition division's decision be set aside and that the patent be revoked in its entirety. It also submitted new document D11.

V. The patent proprietor (respondent) replied by letter of 6 September 2013, requesting that the appeal be dismissed and that the patent be maintained as granted (main request) or alternatively according to auxiliary requests 1 to 11, filed with the same letter. It submitted new document D12 and raised objections against the admission of document D11, of new objections under Article 123(2) EPC and of the "new attacks" under Articles 54(2) and 56 EPC by the appellant.

**Auxiliary request 1** differs from the main request in that the following amendments have been inserted into step (c) of claim 1:

"1. ...
(c) ..., and whereby the spatial definition of the array allows the phenotype of each protein to be related directly to its genotype."

**Auxiliary request 2** differs from the main request in that the following amendments have been inserted into claim 1:

"1. ...
(c) ...; and
(d) using the protein in array screening."

**Auxiliary request 3** differs from the main request in that the following amendments have been inserted into claim 1:
"1. ... 
(c) ...; and 
(d) i) bringing one or more test compounds into contact with the protein array and measuring binding of the one or more compounds to the proteins in the array, thereby screening said one or more compounds for biological activity; or 
   ii) bringing one or more proteins, into contact with the protein array, and measuring binding of the one or more specific proteins with the proteins of the array, thereby screening one or more proteins for specific protein-protein interactions; or 
   iii) bringing one or more nucleic acid probes into contact with the protein array, and measuring binding of the probes to the proteins in the array, thereby screening one or more proteins for specific protein-nucleic acid interactions; or 
   iv) bringing the protein array into contact with an antibody library, such that one or more proteins in the protein array bind to at least one antibody in the antibody library, removing any unbound antibodies, and immobilisation of those antibodies bound to proteins in the protein array, thereby producing an antibody array."

Auxiliary request 4 differs from the main request in that the following amendments have been inserted into step (b) of claim 1:

"1. ... 
(b) expressing the individual tagged proteins in non-bacterial host organisms in a spatially separated format; 
...."
**Auxiliary request 5** differs from the main request in that the following amendments have been inserted into step (b) of claim 1:

"1. ...
(b) expressing the individual tagged proteins in a spatially separated format, wherein the marker moiety is post-translationally modified;
...."

Claim 1 of **auxiliary request 6** differs from claim 1 of auxiliary request 5 in that a further amendment has been inserted:

1. ...
(b) ..., wherein the marker moiety is post-translationally modified by addition of a biotin or lipid molecule;
...."

**Auxiliary requests 7 to 11** combine the amendments of auxiliary requests 2 to 6, respectively, with the amendments of auxiliary request 1.

VI. Two rounds of replies from both parties ensued, with the appellant requesting that document D11 be admitted into the proceedings and document D12 as well as the auxiliary requests filed by the respondent not be admitted, and the respondent requesting that novelty objections based on D2 not be admitted.

VII. Summons to oral proceedings before the board were issued, followed by a communication from the board providing a preliminary opinion on procedural issues.
VIII. By letter of 29 May 2018 the appellant withdrew its request for oral proceedings and announced that nobody would attend the oral proceedings on its behalf. By letter of 19 June 2018, the respondent informed the board that nobody would attend the oral proceedings on its behalf either.

IX. Oral proceedings before the board took place in the absence of both parties. At the end of oral proceedings the chairman announced the board's decision.

X. The appellant's submissions where relevant to the present decision may be summarised as follows:

The passage on page 37, lines 26 to 28, did not constitute a basis for step (b) of claim 1, because it was part of an example and it was not possible under Article 123(2) EPC to take isolated features from examples. Moreover, this feature could not be considered implicitly disclosed because the disclosure of page 5, lines 10 to 13, encompassed the expression both in a non-spatially separated format, as performed in Examples 1 to 4, and in a spatially separated format, as performed in Example 5. While it might have been obvious to express the proteins in such a spatially separated format, obviousness was not the standard for Article 123(2) EPC.

As to step (c) of granted claim 1, claim 3 as filed taught that purification could be performed before or after immobilisation of the tagged proteins in the array, while claim 7 as filed was not directed to the process for producing an array but to the array itself. From page 3, lines 23 to 26, it could only be concluded that purification and immobilisation through the tag took place downstream, meaning after introduction of
the tag, but not necessarily after the proteins had been immobilised in the array. The application as filed in fact taught to purify the proteins first and then apply them to the microarray (page 5, lines 10 to 12; passage deleted from the granted patent). Also, the term "spatially defined format" was not disclosed in the application as filed, and it was broader than the concept "array". Moreover the feature of "specific interactions between the tag and the solid support" was not disclosed either, and the specific disclosure of Example 5 could not serve as a basis for this intermediate generalisation.

XI. The respondent's arguments where relevant to the present decision may be summarised as follows:

While the new objection against step (b) was new and should thus not be admitted, there was a basis for this step in the application as filed because it was clear that, when making an array for use in screening, expression had to be carried out in a spatially separated format: page 4, lines 9 to 11; page 5, lines 10 to 12; page 6, line 26, to page 7, line 5; Example 5 at page 37, line 26, to page 38, line 8; Example 2 at page 27, lines 26 to 28; Example 3, at page 28, last line, to page 29, line 2, and page 29, lines 19 to 21. As there was a generic basis for this feature, this was not a generalisation from the examples. Page 5, lines 10 to 13, did not teach expression in a non-spatially defined format, and Examples 1 and 4 were not related to making a protein array. Steps (a) and (b) essentially reflected the state of the art of making protein arrays, and page 2, lines 15 and 16, specifically taught to "individually clone, express, purify and immobilise all proteins expressed in the specific proteome" or else from cDNA libraries (page 3,
lines 8 to 10); reference to specific immobilisation and purification of individual proteins was again made at page 3, lines 14 to 19 and 23 to 26, rendering it implicit that expression of the individually tagged proteins had to occur in a spatially separate format in order to achieve a spatially defined array of individual proteins.

As to step (c), claims 7, 6 and 3 as filed provided a basis for immobilising and purifying the individual proteins of an array on a solid surface by means of the tag moiety. Also page 3, lines 22 to 26, unambiguously disclosed using the tag to allow "commonality" as well as specificity for both immobilisation and purification. A further basis was found on page 3, lines 14 to 18; page 4, line 22; page 5, line 12; page 6, lines 2 to 5. Moreover, the use of the tag to immobilise and purify the proteins on the solid support of the array was illustrated in Example 5, at page 34, line 26, to page 35, line 2, and page 37, line 28, to page 38, line 1. There was also disclosure in Example 3, at page 28, line 26, and page 29, lines 19 to 23; Example 2, at page 27, line 26, to page 28, line 1; Example 1, at page 25, line 25, to page 26, line 9. The feature "spatially defined format" was disclosed at page 3, lines 22 to 26; page 4, lines 9 to 11; and page 34, lines 27 to 29. The feature "specific interactions between the tag and the solid support" was disclosed on page 3, lines 23 to 26; claims 7 and 6 as filed; page 3, lines 14 to 18; page 4, line 22; page 5, line 12; page 6, lines 2 to 5; Examples, in particular Example 5 at page 37, line 28, to page 38, line 1, Example 3 at page 29, lines 19 to 23, Example 2 at page 27, lines 26 to 29; page 4, lines 18 to 20. The method disclosed e.g. in Example 5 represented a specific embodiment and was mentioned to illustrate the general teaching of the
description, but the examples were not relied on as a basis for the claims as granted.

XII. The parties' requests in their written submissions were understood by the board as follows:

The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety. It also requested that document D11 be admitted into the appeal proceedings and that document D12 and the auxiliary requests filed by the respondent not be admitted.

The respondent requested that the appeal be dismissed, i.e. that the patent be maintained as granted (main request), or alternatively that the patent be maintained in amended form on the basis of one of the sets of claims filed as auxiliary requests 1 to 11 with the reply to the statement of grounds of appeal dated 6 September 2013. It also requested that the following not be admitted into the appeal proceedings:
- document D11,
- inventive step as a ground for opposition, and
- the appellant's objection under Article 123(2) EPC relating to claim 1, step (b).

Furthermore, it requested that, of the appellant's lines of argument concerning lack of novelty and lack of inventive step, only the line based on document D1 for lack of novelty and, if the ground for opposition of inventive step were admitted into the proceedings, the line based on the combination of documents D1 and D10 for lack of inventive step be admitted into the proceedings.
Reasons for the Decision

1. The appeal is admissible.

2. Both parties had been duly summoned but decided not to attend. In accordance with Rule 115(2) EPC the board decided to continue the proceedings in their absence.

Moreover, pursuant to Article 15(3) RPBA the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned. Accordingly, the absent parties were treated as relying only on their written cases.

3. Main request - Article 100(c) EPC

3.1 According to Article 123(2) EPC the European patent application or European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. Hence any amendment to the claims of a European patent application can only be made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the documents as filed (G 2/10, OJ EPO 2012, 376, Reasons 4.3).

3.2 The appellant raised objections under Article 100(c) EPC against claim 1 as granted, essentially arguing that no basis could be found in the application as filed for steps (b) and (c) of the method claimed or for the combination of steps now in the claim.
Claim 1, step (b): "expressing the individual tagged proteins in a spatially separated format"

3.3 The respondent argued that the objection regarding step (b) was new and should therefore not be admitted into the appeal proceedings, and it referred to a number of passages in the application as filed: page 4, lines 9 to 11; page 5, lines 10 to 11; page 6, line 26, to page 7, line 5; Example 5 at page 37, line 26, to page 38, line 8; Example 2 at page 27, lines 26 to 28; Example 3 at page 28, last line, to page 29, line 2, and at page 29, lines 19 to 21.

3.4 As regards admission of the objection against step (b) of claim 1, the board notes that, although it does indeed appear from the file that the appellant had not raised this particular objection at the proceedings before the opposition division, the fact is that the opposition division's decision explicitly discusses a basis for this part of the claim (section 2.4 on page 7 of the appealed decision) and concludes that there was a basis. Accordingly, the discussion of added subject-matter also as regards step (b) of claim 1 was already part of the proceedings before the opposition division, and it is legitimate for the appellant to contest the opposition division's conclusions in this context too. It is further noted that the appellant had already raised this objection in its statement of grounds of appeal (point 4.1.3), i.e. at the earliest stage of the appeal proceedings. The board therefore decided not to exclude this objection from the appeal proceedings under Article 12(4) RPBA.

3.5 As to the existence of a basis in the application as filed for step (b) of claim 1, the board notes that this step is not part of claim 1 as filed, which
disclosed "expressing one or more proteins as full length proteins which are each tagged..." and not "expressing the individual tagged proteins in a spatially separated format". The opposition division came to the conclusion that there was no "expressis verbis" basis for step (b) of claim 1, but considered that it was "implicitly disclosed as it corresponds to what the skilled person usually performs when generating an array in that context", and further indicated page 37, lines 26 to 28, as an example (section 2.4 of the appealed decision).

3.6 The board disagrees with these conclusions of the opposition division. While page 2, lines 15 to 16, explicitly discloses the possibility to "individually clone, express, purify and immobilise all proteins expressed in the specific proteome", this statement is made in a very general context describing production of proteome arrays, and there is not even any indication that the proteins are tagged; it does not provide a basis for a combination of step (b) with the other steps of claim 1. The same is true of the passage on page 3, lines 8 to 10, which in fact relates to "non-specific immobilisation". As is apparent e.g. from page 3, lines 22 to 26, of the application as filed, first the tagged proteins are expressed (but without any indication that "individual tagged proteins" should be expressed "in a spatially separated format") and then their tag is used for "downstream immobilisation and purification procedures" (downstream in relation to the protein expression), "which in turn enables the creation of spatially defined arrays in which many thousands of proteins from a given proteome are displayed"; a similar disclosure is present on page 3, lines 14 to 19. None of the further passages of the general part of the description indicated by the
respondent discloses expression of individual tagged proteins in a spatially separated format either. They either refer to the array itself (i.e. the product obtained by the methods of the invention) as having a spatially defined format (e.g. page 4, lines 9 to 11; page 6, line 26, to page 7, line 5) or refer to "proteins expressed from the cDNA library", which "once purified (...) can be attached to microarrays" (page 5, lines 10 to 12). As to the passages from the Examples, including the passage indicated by the opposition division (page 37, lines 26 to 28), they cannot constitute a basis either, because they disclose examples, taken from particular embodiments, of possible formats which might be considered "spatially separated format": "96 well plates" (Example 2 at page 27, lines 26 to 28), "microwell" (Example 3 at page 29, lines 19 to 21), "96-deep-well blocks" (Example 5 at page 37, lines 26 to 28); they are therefore not suitable as a basis for any possible "spatially separated format" as in step (b) of claim 1. There is thus no explicit disclosure of this feature in the application as filed and, contrary to the opposition division's conclusions, there is no implicit disclosure either; while it might have been obvious for the skilled person, based on common general knowledge, to consider expressing the tagged proteins in a spatially separated format, this is not the same as an implicit, unambiguous disclosure, as required for the purposes of assessing whether there is added subject-matter pursuant to Article 100(c) EPC.

Claim 1, step (c): "purifying and immobilizing each tagged protein in a spatially defined format to produce a protein array on a solid support, whereby specific interactions between the tag and the solid support are used in both said purifying and immobilizing"
3.7 The respondent indicated claims 3, 6 and 7 as filed, as well as a number of passages of the description, as a basis for step (c) of granted claim 1.

3.8 Claim 3 as filed, dependent on claim 1, is directed to a "method of generating a protein array, which comprises cloning and expressing one or more proteins as full length proteins which are each tagged at either the N-or C-terminus with a marker moiety" (claim 1), "wherein the tag allows for purification of the individual proteins in the array" (claim 3). As to claims 6 and 7 as filed, these are dependent on claim 5 and are not directed to a method of generating a protein array (as in granted claim 1), but instead are directed to a protein array: the "array prepared by a method as defined in any one of claims 1 to 4" (claim 5) is further defined such that "the components of the array are immobilised, eg to a solid surface" (claim 6) and "the individual proteins are immobilised by means of the tag moiety" (claim 7).

3.9 The respondent also indicated passages of the general part of the description as filed as constituting a basis for granted claim 1. Page 3, lines 14 to 18, states that "the ability to create a functional proteome array in which individual proteins are specifically immobilised and purified via a common motif or tag without affecting function and without requiring knowledge of the entire genome sequence would therefore represent a huge advance in the field of functional proteomics", while lines 22 to 26 of the same page read: "This 'tag' can then be used to impart a commonality and specificity to downstream immobilisation and purification procedures, which in turn enables the creation of spatially defined arrays
in which many thousands of proteins from a given proteome are displayed". Page 4, lines 21 to 22, reads: "In a preferred embodiment, the marker moiety would also allow purification of 'tagged' proteins". Page 5, line 12, reads that "Attachment can be effected by means of the tag itself" but goes on to state that attachment may be effected "alternatively, by means of another moiety which is first attached to the proteins". Finally, page 6, lines 2 to 5, reads: "Compared to the former, the method of immobilising proteins in an array as described herein is through specific rather than non-specific interactions, and these specific interactions are a function of the tag added to the termini of each cDNA".

3.10 The respondent also mentioned passages belonging to the Examples, in particular on page 27, line 28, to page 28, line 1; page 30, lines 24 to 26; and page 34, lines 27 to 29. The first of these passages is part of Example 2 and reads: "As in Example 1, we have been able to demonstrate the specific immobilisation of the fusion proteins via these tags, (...)". The passage on page 30, lines 24 to 26, is part of Example 3 and reads: "a positive signal in the assay can only be observed if the NF-κB p50-DNA interaction is maintained on immobilisation of NF-κB p50 via the tag; (...)". As to the passage on page 34, lines 27 to 29, it is part of Example 5 and reads: "We have generated arrays of the resultant specifically modified proteins such that each position in the array corresponds to a single recombinant protein immobilised through the tag appended as a result of this procedure" (page 34, line 27, to page 35, line 1).

3.11 The board fails to see where a basis is to be found in the application as filed for a method with all the
steps as defined in granted claim 1, and in particular with step (c). Claims 1 to 3 as filed defined the method only as comprising cloning and expressing one or more proteins as full-length proteins which are each tagged at either the N- or C-terminus with a marker moiety, wherein the tag allows for purification of the individual proteins in the array. Claims 5 to 7 as filed were not directed to the method but to the protein array itself, which was prepared by the method of claims 1 to 4 (claim 5): they specify that the components of the array are immobilised, e.g. to a solid surface (claim 6), by means of the tag moiety (claim 7). The passage on page 3, lines 22 to 26, teaches that, through the tag, which allows specific immobilisation and purification procedures, it is possible to create "spatially defined arrays": it does not describe a specific step; it relates at most to a characteristic of the resulting array obtained by the method. Moreover, the feature "whereby specific interactions between the tag and the solid support are used in both said purifying and immobilizing" also lacks a basis. The indicated passage on page 6, lines 2 to 5, refers to immobilising (not purifying) and merely refers in general terms to specific interactions, not to specific interactions between the tag and the solid support. Finally, the cited passages of the Examples illustrate the use of the tag for immobilisation but not for purification, and the board fails to see how these passages provide a basis for step (c) of claim 1 as granted: in fact, none of the Examples discloses a method comprising all the steps as now in the claim, and the respondent has explicitly stated that it does not rely on the examples as a basis for the granted claims (letter of 3 April 2014, page 4, first paragraph).
3.12 Thus, the ground for opposition under Article 100(c) EPC prejudices the maintenance of the patent as granted.

4. **Auxiliary requests 1 to 11**

4.1 **Admission**

4.1.1 The appeal proceedings are intended to review the correctness of the first-instance decision rather than to continue examination by other means. Thus, pursuant to Article 12(4) RPBA, it is at the discretion of the boards of appeal to hold inadmissible requests submitted with the statement of grounds of appeal or the reply thereto which could have been presented in the proceedings before the examining or opposition division. When exercising their discretion, the boards take into account the circumstances of the particular case and the arguments put forward by the parties.

4.1.2 Auxiliary requests 1 to 11 were all filed with the respondent's reply to the statement of grounds of appeal and thus are part of the submissions provided for under Article 12(2) RPBA. Moreover, as argued by the respondent, auxiliary requests 1, 3, 4 and 5 correspond to requests that had also been filed during the first-instance proceedings and are therefore not new requests. Auxiliary requests 2 and 6, on the other hand, were submitted in reaction to new arguments concerning novelty that were presented by the appellant for the first time with its statement of grounds of appeal, and therefore they could not have been submitted earlier. As to auxiliary requests 7 to 11, these merely combine the amendments made to auxiliary request 1 with those made to auxiliary requests 2 to 6, respectively.
4.1.3 In view of the respondent's submissions, the board does not agree with the appellant's argument that the auxiliary requests should not be admitted into the proceedings. Moreover, it cannot identify a specific situation in the proceedings before the opposition division in which the respondent would have been expected to file these specific claim requests as an auxiliary measure. In this context it also takes into consideration that the opposition division's decision, in line with its provisional opinion, was to reject the opposition. Auxiliary requests 1 to 11 are thus admitted into the appeal proceedings pursuant to Article 12(4) RPBA.

4.2 **Article 123(2) EPC**

4.2.1 Claim 1 of all of these requests contains steps (b) and (c) of the method as claimed in claim 1 of the main request, and the further characterisation by additional features does not serve to overcome the deficiencies under Article 123(2) EPC.

4.2.2 As regards auxiliary request 1, the respondent argued that the added feature in claim 1 "the spatial definition of the array allows the phenotype of each protein to be related directly to its genotype" implied that the individually tagged proteins had to be immobilised on the solid support of the array in a spatially defined format so that it was possible to determine which protein the compound being screened bound to. While this may be true, the problem remains that, for the reasons given above, there is no basis for the feature whereby the proteins have to be expressed in a spatially separated format (step (b) of granted claim 1).
4.2.3 In auxiliary requests 2 to 3, the additional features in claim 1 relate to downstream uses of the obtained protein array and are therefore not limiting for steps (b) and (c). In auxiliary requests 4 to 6, the additional features in claim 1 further define step (b), but the underlying lack of a basis for the step of expressing individual tagged proteins in a spatially separated format still remains, while step (c) is unchanged in relation to step (c) of the main request.

4.2.4 The same reasoning applies to claims 1 of auxiliary requests 7 to 11, which combine the amendments of auxiliary requests 2 to 6 with the amendments of auxiliary request 1.

4.2.5 Hence for the same reasons as discussed above for the main request, claim 1 of each of auxiliary requests 1 to 11 also contravenes Article 123(2) EPC.
Order

For these reasons it is decided that:

1. The appealed decision is set aside.

2. The patent is revoked.

The Registrar: 

The Chairman: 

M. Kiehl  

A. Lindner 

Decision electronically authenticated