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**Datasheet for the decision  
of 28 October 2019**

**Case Number:** T 1663/15 - 3.3.08

**Application Number:** 09774904.8

**Publication Number:** 2379718

**IPC:** C12N15/10, C12N15/81, C40B40/08

**Language of the proceedings:** EN

**Title of invention:**  
YEAST DISPLAY SYSTEMS

**Patent Proprietor:**  
Novartis AG

**Opponent:**  
OLSWANG LLP

**Headword:**  
Yeast display systems/NOVARTIS

**Relevant legal provisions:**  
EPC Art. 54, 56, 83, 123(2)  
RPBA Art. 12(4)

**Keyword:**  
"Main Request - requirements of the EPC met (yes)"

**Decisions cited:**

T 0305/87

**Catchword:**



**Beschwerdekammern**  
**Boards of Appeal**  
**Chambres de recours**

Boards of Appeal of the  
European Patent Office  
Richard-Reitzner-Allee 8  
85540 Haar  
GERMANY  
Tel. +49 (0)89 2399-0  
Fax +49 (0)89 2399-4465

Case Number: T 1663/15 - 3.3.08

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.08**  
**of 28 October 2019**

**Appellant:** OLSWANG LLP  
(Opponent) 90 High Holborn  
London  
Greater London WC1V 6XX (GB)

**Representative:** Stephen, Robert John  
CMS Cameron McKenna Nabarro  
Olswang LLP  
Cannon Place  
78 Cannon Street  
London EC4N 6AF (GB)

**Respondent:** Novartis AG  
(Patent Proprietor) Lichtstrasse 35  
4056 Basel (CH)

**Representative:** Adams, Harvey Vaughan John  
Leathley, Anna  
Carpmaels & Ransford LLP  
One Southampton Row  
London WC1B 5HA (GB)

**Decision under appeal:** **Interlocutory decision of the Opposition  
Division of the European Patent Office posted on  
22 June 2015 concerning maintenance of the  
European Patent No. 2379718 in amended form.**

**Composition of the Board:**

<b>Chairman</b>	B. Stolz
<b>Members:</b>	D. Pilat
	J. Geschwind

## **Summary of Facts and Submissions**

- I. European patent N° 2 379 718 is based on European patent application N° 09774904.8 hereinafter "the patent application" and was opposed on the grounds of Articles 100 (a), (b) and (c) EPC. The opposition division considered the main request not to fulfil the requirements of Article 54 EPC, whereas auxiliary request 1 was held to fulfil the requirements of the EPC.
- II. The appellant (opponent) lodged an appeal against the opposition division's decision, raised objections under Articles 123(2), 83, 54 and 56 EPC and filed new document D12 in support of its case.
- III. In reply thereto, the respondent (patent proprietor) filed new auxiliary requests 1, 2, 2A, 3, 3A, 3B, 3C, 4, 4A, 4B, 4C, 5, 5A, 5B, 5C, 6, 6A, 6B, 6C, 7, 7A, 7B, 7C, 8, 8A, 8B, 8C, 9, 9A, 9B, 9C, 10, 10A, 10B, 10C, 11, 12 and 13.
- IV. The parties were summoned to oral proceedings. In a communication pursuant to Article 17(1) RPBA, the parties were informed of the board's provisional, non-binding opinion on some of the legal and substantive matters of the case.
- V. In reply to the board's communication, the appellant, without providing substantive arguments, announced that it would not attend the oral proceedings.
- VI. The respondent replied to the board's communication by filing further observations on inventive step and submitted auxiliary request 14.

VII. Oral proceedings were held on 28 October 2019 in the absence of the appellant.

VIII. Independent claims 1, 17 and 18 of the main request read as follows:

"1. A library of host cells, wherein each host cell comprising:

(a) a cell surface molecule attached to the surface of the cell,

(b) an adapter molecule comprising a first binding site and a second binding site, and

(c) a display molecule comprising a modified polypeptide, wherein the modified polypeptide is selected from the group consisting of: a scaffold protein, a signal transduction protein, an antibody, an immunoglobulin, an immunoadhesin, a receptor, a ligand, an oncoprotein, a transcription factor, an enzyme, and a fibronectin polypeptide;

wherein the first binding site binds specifically to the cell surface molecule and cannot bind to the display molecule and the second binding site binds specifically to the display molecule and cannot bind to the cell surface molecule,

wherein the adapter molecule is not a component of the modified polypeptide, and wherein each host cell comprises a different modified polypeptide.

17. A method for displaying a modified polypeptide comprising;

(a) providing a host cell comprising a cell surface molecule attached to the surface of the cell which is expressed from an expression vector in the host

cell and a first nucleic acid encoding a display polypeptide comprising a modified polypeptide, wherein the modified polypeptide is selected from the group consisting of: a scaffold protein, a signal transduction protein, an antibody, an immunoglobulin, an immunoadhesin, a receptor, a ligand, an oncoprotein, a transcription factor, an enzyme, and a fibronectin polypeptide,

(b) contacting the host cell with an adapter molecule comprising a first binding site and a second binding site under conditions wherein the first binding site binds to the cell surface molecule, and

(c) incubating the host cell under conditions wherein the host cell exports the display polypeptide outside the host cell under conditions wherein the second binding site binds to the display polypeptide,

wherein the first binding site binds specifically to the cell surface molecule and cannot bind to the display molecule and the second binding site binds specifically to the display polypeptide and cannot bind to the cell surface molecule, and wherein the adapter molecule is not a component of the modified polypeptide.

18. A method for generating a host cell display library comprising:

introducing into a plurality of host cells a display library of first nucleic acids each encoding a display polypeptide comprising a modified polypeptide, wherein the modified polypeptide is selected from the group consisting of: a scaffold protein, a signal transduction protein, an antibody, an immunoglobulin, an

immunoadhesin, a receptor, a ligand, an oncoprotein, a transcription factor, an enzyme, and a fibronectin polypeptide, wherein at least two of the introduced first nucleic acids encode different modified polypeptides, wherein each host cell comprises a second nucleic acid which encodes a cell surface polypeptide and a third nucleic acid which encodes an adapter molecule comprising a first binding site and a second binding site, wherein the first binding site binds to the cell surface molecule but not the display polypeptide and the second binding site binds to the display polypeptide but not the cell surface molecule, and wherein the adapter molecule is not a component of the modified polypeptide."

Dependent claims 2 to 16 define specific embodiments of the library of claim 1.

IX. The following documents are cited in this decision:

- D2 WO2008/118476 (published on 2 October 2008);
- D5 J.M. Weaver-Feldhaus et al., 2004, "Yeast mating for combinatorial Fab library generation and surface display", FEBS letters, vol. 564, pages 24-34;
- D7 E.T. Boder and K.D. Wittrup, 1997, "Yeast surface display for screening combinatorial polypeptide libraries", Nature biotechnology, vol. 15, pages 553-557;
- D10 M.E. Kimple et al., 2001, "Functional relevance of the disulfide-linked complex of the



N-terminal PDZ domain of InaD with NorpA", The EMBO Journal, vol. 20, N°16, pages 4414-4422;

D12 WO2007/130520 (published on 15 November 2007).

- X. The appellant's written submissions, insofar as relevant to the present decision, may be summarized as follows:

Admission of document D12 into the appeal proceedings

Document D12 was filed in response to the respondent's arguments, submitted during oral proceedings in opposition, that document D2 disclosed only a system which first lacked variability in the correct orientation and second that a display molecule had indeed both a modified polypeptide component and an additional component binding to the adapter. Appellant could not have filed document D12 earlier than with its statement of grounds of appeal.

Article 123(2) EPC

No reason was given why the decision under appeal was wrong. The statement of grounds of appeal merely referred to facts and evidence put forward under Article 123(2) EPC in the notice of opposition.

Article 83 EPC

Paragraph [0039] of the patent application identified an immunoglobulin as a display molecule, wherein a part of the immunoglobulin represented a modified polypeptide and another part the adapter binding part. However, there was no teaching in the patent which part of an immunoglobulin might be acceptably bound to an

adapter or act as an adapter binding site, and which part of the immunoglobulin might be considered as the modified polypeptide. The patent did not disclose which parts of the immunoglobulin (display molecule) and how much of the immunoglobulin chain were necessary for a modified polypeptide to display variability and to remain unaffected by an adapter bound to its adapter binding part.

Article 54 EPC

The subject-matter of claim 1 lacked novelty over documents D2 and D5. Although claim 1 was limited to a library of host cells, wherein the modified polypeptide was selected from the group consisting of, *inter alia*, an antibody and an immunoglobulin, this feature could not confer novelty. Document D2 disclosed a cell having a first binding partner at the cell surface, a target molecule linked to a second binding partner, where the second binding partner was bound to the first binding partner (see page 29, lines 1-19). In a particular embodiment "the target or substrate molecule linked to a second binding partner may be immobilized on the host cell surface through binding of the second binding partner to a suitable first binding partner attached to the cell surface." Hence, the target or substrate molecule linked to biotin provided a polar adapter molecule binding directionally avidin on the host cell surface. The target or substrate molecule corresponding to the display molecule of claim 1 could be, for example, an antigen, an epitope, a ligand, a substrate etc., having a binding specificity and interacting with an engineered protein, such as an antibody, an antibody fragment, or an antibody-like polypeptide, a receptor, an antigen ... etc. (see page 3, lines 18 and 25, page 5, line 34, page 17, line 16 and page 22, line 20; page

28, lines 17-27). Such binding was specific and directional. Document D2 related further to methods for displaying an engineered protein on a host cell surface, wherein engineered proteins were secreted and retained on the surface of the host cells and in some embodiments the target molecule was immobilized to the cell surface (see pages 1 and 2, bridging and 2nd paragraph and page 9, lines 4 to 12, page 29, lines 1 to 20). Since it disclosed specifically an antigen tethered to the cell surface and an antibody binding the antigen via its variable region, it provided a library of host cells expressing antibodies bound with different affinities to the target antigen. Thus, host cells expressing the engineered proteins specifically binding the antigen could be screened and detected. Both the outside-facing Fc portion and the inward-facing free second Fab arm of the engineered antibody remained accessible for detection. Document D2 figure 5F disclosed further a system of three components in which an engineered protein directionally bound to avidin at the cell surface. Since the second binding site of the adapter molecule and the display molecule could be covalently linked, as set out in claim 6 of the opposed patent, a pre-existing specific binding via non-covalent interactions was not an implicit feature of claim 1.

Thus, independent claims 1, 17 and 18 lacked novelty in view of the general teaching of document D2, in particular Figure 5F, page 29, lines 1 to 20, and page 57, first paragraph.

Since the specific binding of the second binding site of the adaptor molecule encompassed a covalent linkage, including for example a peptide bond, also document D7 deprived claim 1 of novelty.

Article 56 EPC

Document D2 or, in the alternative document D10, represented the closest prior art for the subject-matter of claim 1.

Document D2 related to compositions and methods for displaying an engineered protein on a host cell surface or generating a library of engineered proteins on a cell surface.

The only difference between the general teaching of document D2, especially on page 29, was that it did not disclose a library of cells comprising a display molecule with an outwards variability. The claims' wording did however not require an outward facing variability for the display molecules to be screened.

The purpose of document D2 was to express engineered polypeptides to bind a target molecule on the cell surface (see embodiment on page 29, lines 1 to 19). Where the engineered polypeptide was a single antibody chain, some incapable of binding the target molecule displayed on the cell surface, the skilled person would have screened the library of cells to detect those comprising an engineered polypeptide bound on its surface. If the antibody chains were capable of binding the target molecule, the skilled person would have obviously screened either for the outward facing Fc variability or its inward-facing free second Fab arm.

Thus, it was obvious to make a library screenable for binding of the engineered polypeptide to the target. Thus, claim 1 lacked an inventive step over document D2 alone. Since document D2 taught that the elements of the three component system could be encoded on

expression vectors, the methods of claims 17 and 18 lacked an inventive step as well.

XI. The **respondent's** written submissions, insofar as relevant to the present decision, may be summarized as follows:

Admission of document D12 into the appeal proceedings

The arguments that the system described in document D2 first lacked a pre-existing variability in the correct orientation, in other words with the required polarity, and second did not describe a display molecule having both a modified polypeptide component and an additional component binding to the adapter was not raised for the first time during oral proceedings in opposition but was presented on page 3 and in the discussion on page 4 of the patentee's reply to the opposition brief. Hence, document D12 could have been filed earlier.

Article 123(2) EPC

The patentee's arguments put forward under Article 123(2) EPC on page 2 of the reply to the opposition dated 7 August 2014 were still valid and maintained.

Article 83 EPC

Appellant's objection for lack of sufficient disclosure could only be relevant if serious doubts substantiated by verifiable facts had been provided showing that the invention could not be reproduced based on the teaching of the patent. On the contrary, the patent disclosed embodiments falling under the scope of claim 1 and how to carry out the invention (see example 1). Since no doubts substantiated by verifiable facts were provided

there was no reason to consider that the claimed subject-matter could not be reproduced. Appellant's objection under Article 83 EPC was based on an unsubstantiated speculation (see decision T19/90).

#### Article 54 EPC

Document D2 on page 29 related to the polarity of the adapter molecule (see Figures 5 and 6). Figure 5 described only a two component system in which the polar molecule was the expressed protein of interest fused to the BAP as confirmed by Figure 5's legend. Figure 6 showed a polar adapter molecule and a binding antigen which was the only possible display molecule according to the wording of claim 1. However, the antigen was not different in each cell (cf. Figure 6's legend). Thus, none of the recited passages in document D2 disclosed a polar adapter molecule in combination with the other two members of the three component system as required by claim 1, let alone incorporated in a library of cells.

The binding via a peptide bond between an adapter molecule and a display molecule as illustrated in Figure 5F could not be considered a specific binding in the light of the disclosure of the patent.

The meaning of the terms in claim 1 had to be determined to assess whether example 3 and/or Figure 9 of document D2 and of Figure 1 of document D5 were novelty destroying.

First, the adapter molecule of claim 1 could not be a "component of the modified polypeptide" meaning that configurations where the modified polypeptide was a naturally occurring binding partner of the adapter

molecule were excluded, but configurations where a portion of the display molecule was a naturally occurring binding partner of the adapter molecule were allowed. Second, the display molecule comprised a modified polypeptide that had to be different in each host cell and had to comprise another part binding to the adapter molecule (see patent Figure 1; [0030] line 22 to 23 and [0031]).

It followed that a construct comprising a light chain of IgG-A or IgG-B (binding antigen A or B respectively) as the modified polypeptide, and a heavy chain as the adapter molecule, as described in example 3 and Figure 9 of document D2, and in Figure 1 of document D5 were explicitly excluded from the wording of claim 1. Documents D2 and D5 did not deprive claim 1 of novelty.

The three variable non-consecutive CDR sequences within the variable portion of the immunoglobulin light chain or heavy chain could not be regarded as "the modified polypeptide" (singular) of a display molecule that varied from cell to cell. Thus, the modified polypeptide of the display molecule could only mean the whole variable portion of an immunoglobulin light or heavy chain or the light or heavy chain itself. The modified polypeptide disclosed in example 3 and Figure 9 of document D2 and Figure 1 of document D5 could therefore only be the variable portion of the immunoglobulin light or heavy chain. Since the modified polypeptide was a naturally occurring binding partner of the adapter molecule, these constructs were excluded from claim 1.

The same conclusion applied mutatis mutandis to claims 17 and 18.

Document D5 described a system in which antibody chains were expressed in yeast. Haploid yeast were created and mated. The resulting diploid yeast cells expressed an antibody heavy chain fused to Aga2 which associated with Aga1 fused to an antibody light chain. The Vk and Vh portions of these fusion proteins were stated to vary. Since Figure 1 of document D5 described a light chain, corresponding to the modified polypeptide of claim 1, that bound a heavy chain fused to Aga2, corresponding to the adapter molecule of claim 1, but said adapter and the modified polypeptide were naturally occurring binding partners, the embodiment of Figure 1 was excluded from claim 1.

Document D7 did not deprive claim 1 of novelty as the specific binding by means of a peptide bond was at odds with the teaching of the patent which described that host cells secreted or excreted the display molecule with a pre-existing binding affinity prior to its binding to the adapter molecule on the cell surface (see patent [0025]). A display molecule linked by a peptide bond to the adapter molecule could only be regarded as a fusion protein but not as specifically binding an adaptor molecule.

Article 56 EPC

Document D2 represented the closest prior art for the subject-matter of claim 1.

In view of document D2 the problem to be solved could be defined as the provision of a modular surface display library to be queried which does not have side reactions such as cell-cell interactions.



The solution to this technical problem was the library of claim 1.

The library of claim 1 comprised a polar adapter molecule and required the modified polypeptide of the display molecule to be different in each host cell.

The solution of claim 1 was not obvious over the embodiments of document D2, because the prior art described two component systems and because the modified polypeptide of claim 1 had to be different in each host cell. Following the teaching in document D2, especially the embodiment disclosed on page 29, lines 1 to 19, variability was only found in the polar adapter molecule (see e.g. the Figure legends for Figures 5 and 6), while in figure 6 the third component, the antigen to be screened, was nowhere described to be variable and as such not depriving claim 1 of novelty. Even if the two component systems allowed for variability in a library to be screened, the system with three components was the outcome of a screening and its re-"screening" was nowhere disclosed in document D2 (e.g. to see whether binding of a molecule had occurred).

XII. The appellant requested that the decision under appeal be set aside, and that the patent be revoked in its entirety. It further requested to admit document D12 into the appeal proceedings.

XIII. The respondent requested that the appeal be dismissed or alternatively the patent be maintained on the basis of one of the newly filed auxiliary requests, and that document D12 not be admitted into the appeal proceedings.

## **Reasons for the Decision**

1. The duly summoned appellant did not attend the oral proceedings, which in accordance with Rule 115(2) EPC and Article 15(3) RPBA took place in its absence.

*Admission of document D12 into the proceedings (Article 12(4) RPBA 2007)*

2. According to the established case law, appeal proceedings are not an opportunity to re-run the proceedings before the first instance; the function of an appeal is to give a judicial decision upon the correctness of a separate earlier decision taken by a department of first instance (cf. "Case Law of the Boards of Appeal", 9th edition 2019, V.A.1, 1133). Article 12(4) RPBA 2007 empowers the board not to consider facts, evidence or requests that could have been presented in the first instance proceedings.
3. The appellant submitted document D12 with its statement of grounds of appeal in response to one of respondent's arguments that one of the display molecules described in document D2 could not be screened. As this argument was first brought forward by the respondent during oral proceedings in opposition, appellant could not have filed document D12 earlier.
  - 3.1 In its communication in preparation of the oral proceedings, the board indicated that document D12 was unlikely to be admitted because said argument raised during oral proceedings in opposition had initially been raised in the respondent's reply to the opposition brief (cf. page 3 and page 4).

- 3.2 Since the appellant neither provided cogent reasons why document D12 could not have been filed earlier nor attended the oral proceedings, the board exercises its discretion pursuant to Article 12(4) RPBA 2007 and decides not to admit document D12 into the appeal proceedings in the present case.

*Main request*

4. The main request corresponds to Auxiliary request 1 underlying the decision under appeal upon the basis of which the opposition division decided that the patent and the invention to which it relates met the requirements of the EPC.

*Admission of objections raised under Article 123(2) EPC*

5. Concerning its objections under Article 123(2) EPC, the opponent merely stated: "We maintain our arguments on file before the Opposition Division" (see page 1 of the statement of grounds of appeal).
6. In the communication pursuant to Article 17(1) RPBA 2007, the board informed the appellant of its opinion that a mere reference to a party's earlier submissions and/or the verbatim repetition of the arguments presented in these submissions ("grounds by cut-and-paste"), including those submissions or arguments put forward at the oral proceedings before the opposition division, but without actually dealing with, or entering into a discussion of, the reasons given in the decision under appeal by the opposition division for arriving at its decision, was not enough to substantiate a ground of appeal (cf. "Case Law of the Boards of Appeal", 9th edition 2019, V.A.3.2.1.i and V.A.3.2.1.j; also V.A.2.6.3.e, and V.A.2.6.4.a).

7. According to Article 12(2) RPBA 2007, the statement of grounds of appeal shall contain the appellant's complete case. This requirement is not fulfilled by a mere passing reference to facts and evidence put forward in opposition proceedings. It is not for the board to identify issues which arose in opposition proceedings and may (or may not) still be a matter of dispute in appeal proceedings, but for the appellant to put forward in the statement of grounds of appeal its line(s) of argument and each of the facts and evidence on which it relies.

7.1 In view of the reasons given by the opposition division in relation to Article 123(2) EPC (cf. pages 3 to 4, points 1 and 2 of the decision under appeal) and the complete absence of arguments why the opposition division's reasoning was wrong, the board considers objections under Article 123(2) EPC in the appeal proceedings unsubstantiated. The board therefore considers the opposition division's conclusion in respect of Article 123(2) EPC unchallenged and confirms it.

*Article 83 EPC*

8. The appellant submitted that paragraph [0039] of the patent application identified an immunoglobulin as a suitable display molecule. The patent failed however to disclose which part of an immunoglobulin represented the adapter binding site, and which part of the immunoglobulin represented the region to be modified. Thus, it did not disclose in a manner sufficiently clear and complete which parts and how much of an immunoglobulin chain was necessary for a modified polypeptide to adequately display variability and to

remain unaffected by an adapter bound to its adapter binding part.

- 8.1 The issue to be assessed is whether or not the patent provides sufficient information on how to generate a library of host cells according to claim 1 with immunoglobulins as the display molecule without undue burden and/or inventive skills.
- 8.2 In the decision under appeal and in the board's communication pursuant to Article 17(1) RPBA 2007 it was underscored that the appellant failed to cast serious doubts substantiated by verifiable facts with respect to the disclosure of the claimed invention (see item 9 of the board's communication and page 8 of the decision under appeal).
- 8.3 The appellant has not responded to the board's provisional observation in substance.
- 8.4 Since, the examples in the patent provide sufficient guidance on how to carry out the invention and no verifiable facts going beyond mere allegations were provided, the board considers appellant's objection of insufficiency of disclosure to be unpersuasive and the finding in the decision under appeal to be correct.

*Article 54 EPC*

9. Document D2 relates to libraries and components for protein screening, to compositions and methods for displaying an engineered protein on a cell surface and to the generation of protein display libraries (see page 1, lines 15 to 17, and page 1 line 30 to page 2 line 10). It describes a method of generating a library of engineered proteins on host cells, wherein the host

cells display a first binding partner coupled to a target molecule, and wherein each vector comprises a gene encoding a unique engineered protein having binding affinity to said target molecule. In some embodiments a cell displays at the cell surface a first binding partner binding to a second binding partner coupled with a soluble target molecule, thereby immobilizing the target molecule on the cell surface having an affinity for the engineered protein of interest (see page 9, lines 4 to 12; page 29, lines 1 to 20 and page 57, lines 1 to 8). The engineered protein is, through its interaction with a "target molecule", immobilized on the cell surface (see page 28, lines 17 to 27). The "target molecule" may be, for example, an antigen, epitope, ligand, substrate, capable of binding an engineered protein, such as an antibody, receptor, antigen, enzyme etc. (see page 28, lines 17 to 22). More specifically, avidin may act as first binding partner, directly or indirectly displayed, attached, coupled to the host cell surface, whilst biotin, linked to the "target molecule", may act as a second binding partner. Biotin may be directly chemically coupled to the cell surface or indirectly via a suitable linker to the cell surface, for instance via an avidin or an avidin-like protein which may be added extracellularly. Alternatively, an expressed fusion protein comprising avidin or an avidin may be conjugated to the cell wall to which soluble biotin may be added (see page 29, lines 1 to 20).

Document D2 discloses further a method for displaying an engineered protein on the cell surface, wherein the host cell displays a first binding partner on the cell surface that binds a second binding partner coupled to a target molecule. The cell surface immobilized target molecule is then bound by a cell that secretes the

engineered protein (see page 5, lines 24-31). The engineered protein can be an antigen and the target molecule an antibody or fragment thereof or vice versa (see page 3, lines 18 and 25; page 5, line 34; page 17, line 16 and page 22, line 20).

9.1 Document D2 in the above passages offers multiple options, such as "in some embodiments" or "may" or "can" for its first and second binding partners and target molecules, but does not disclose a library of host cells comprising a polar adapter molecule as defined in claim 1, i.e. comprising a first and second binding site, wherein the first binding site binds specifically to the cell surface molecule and cannot bind to the display molecule, and the second binding site binds specifically to the display molecule and cannot bind to the cell surface molecule, even if the specific binding was not excluded to be covalent (see claims 2 and 6). It discloses even less a library of host cells comprising an "adapter molecule" and a "display molecule" as defined in claim 1, e.g. binding to an antibody or being an antibody, where said "display molecule" comprising a modified polypeptide is different in each host cell of the library (see page 3, lines 18 and 25; page 5, line 34; page 17, line 16 and page 22, line 20).

9.2 Even if the generic disclosure of document D2 would suggest that the target molecule and the engineered protein of the display system could be an antigen and an antibody respectively, and the Fc portion of the antibody or its non-engaged Fab arm are exposed, there is no disclosure in document D2 of an embodiment where an antibody bound target molecule is the display molecule to be screened or re-screened for identifying cells of a library of cells that express an antibody

specifically binding to the target antigen. A target molecule (i.e. antigen) recognized by a variable region of an antibody to be screened or re-screened (i.e. display molecule), is bound to have different binding affinities for the target antigen and as such cannot be construed as "the" second binding site (singular) of an adapter molecule binding specifically to the display molecule in the sense of claim 1. The bound antibody in each cell represent a cell surface "displayed" molecule, but not a "display molecule" in accordance with claim 1.

9.3 Figure 5F of document D2 is the only specific disclosure of a three component system. It shows a cell with an engineered biotinylated fusion protein binding to an avidin molecule displayed at the cell surface. Avidin is bound to a cell surface molecule of a host cell (see patent [0027]) and is specifically bound to an adapter molecule - biotinylated BAP - which is specifically bound to a display molecule - labelled as "protein" - by means of a covalent bond, which is an option encompassed by the wording of claim 6 of the opposed patent. Figure 5F neither discloses an engineered protein selected from the list of claim 1, nor that the cell is comprised in a library of cells wherein each host cell displays a different engineered protein. Thus, claim 1 is novel.

10. Document D2 on page 57, first paragraph, discloses that "[I]n some embodiments, host cells may be transfected with a vector encoding a first binding protein (e.g., avidin), a vector encoding an engineered protein of interest having an affinity for a target molecule and a vector encoding a construct comprising a target molecule and a second binding partner". This paragraph, even read in combination with page 29 of document D2,



does not disclose a method of displaying a modified polypeptide comprising the step of providing a host cell comprising a first nucleic acid encoding a display molecule selected from the group consisting of a scaffold protein, a signal transduction protein, an antibody, an immunoglobulin, an immunoadhesin, a receptor, a ligand, an oncoprotein, a transcription factor, an enzyme, and a fibronectin polypeptide, and of contacting the host cell with a specific adapter molecule as defined in claim 17. Thus, the subject-matter of claim 17 is novel.

11. The subject-matter of claim 18 includes at least the same technical features as claim 17 which are however missing in document D2 (see paragraph above). In consequence, for the same reasons as provided above for claim 17, claim 18 is novel over document D2.
  
12. Example 3 and Figure 9 of document D2 disclose an antibody light chain representing a "display molecule" bound to an antibody heavy chain representing an "adapter molecule" which is bound to the cell surface via a "first binding site" provided by a biotin group covalently attached to said adapter molecule comprising the antibody heavy chain. The biotin group is in turn bound to a cell surface molecule. The host cells are transformed with either of two antibody constructs IgG-A or IgG-B, specific for antigen A and B respectively, encoding a heavy chain fused to the N-terminus of the biotin acceptor peptide (BAP) and the light chain fused to the C-terminus of a FLAG tag. The cells expressing IgG-A and IgG-B were mixed to form a library of cells having a ratio of 1:10000. In these constructs only the immunoglobulin or antibody light chains correspond to the display molecule of claim 1. However, they are not

listed in part c) of claim 1 and thus excluded from the scope of protection claimed.

- 12.1 The appellant argued that an isolated light chain fell under the definition of an immunoglobulin. The board disagrees because the term immunoglobulin molecule has an accepted meaning in the art. Light and heavy chains are both components of an immunoglobulin molecule. Since this is generally accepted, there is no need for this term to be re-interpreted in the light of the description. However, even if the the skilled person turned to the description to understand its technical meaning, it would not come to a different conclusion. Furthermore according to claim 1, the adapter molecule is not "a component of the modified polypeptide" and thus not a naturally occurring binding partner of any fragment of the modified peptide. In the present case the light chain molecule is however a naturally occurring binding partner of the heavy chain molecule of an immunoglobulin or antibody which explicitly excludes it from the scope of protection of claim 1 (see paragraph [0033] of the patent).
13. Document D5 discloses how haploid yeast are created and mated resulting in diploid yeast cells expressing a heterodimeric Fab display molecule comprising a heavy chain fused to Aga2 and a light chain disulfide linked to the heavy chain on the cell surface (see Figure 1 and legend). The secreted heavy and light chains associate with each other and bind to the cell via a Aga2/Aga1 interaction. For the reasons given in paragraphs 12 and 12.1 above, the light and heavy chain alone cannot be regarded as an immunoglobulin molecule. Thus, the host cell display system of document D5 does not anticipate the subject-matter of claim 1. For the

same reasons document D5 does not anticipate the methods of claims 17 and 18.

14. Figure 1 of document D7 discloses a three component structure, wherein the adapter is the Aga2p fused to hemagglutinin antigen (HA), wherein Aga2p binds Aga1p and wherein the hemagglutinin antigen is fused to a scFv molecule. Since the scFv molecule does not fall under the definition of an antibody or an immunoglobulin, it cannot be regarded as a modified polypeptide according to claim 1.
15. Thus, documents D2, D5 or D7 do not disclose subject-matter anticipating the subject matter of claims 1, 17 and 18.

*Article 56 EPC*

16. It is common ground that document D2 represents the closest prior art for the subject-matter of claim 1.
17. Document D10 was mentioned as alternative closest prior art but no rationale and arguments has been provided in this respect. For this reason this approach is disregarded.
18. As set out above, document D2 relates to compositions and methods for displaying an engineered protein on a host cell surface. The engineered protein is expressed in a host cell under conditions which result in the protein being modified in such a way that it binds to a surface-immobilized binding partner when secreted from the host cell. Figure 5 and its legend illustrate a display system composed of two separate components, comprising a display molecule labelled as "protein" fused to an adapter molecule consisting of a

biotinylated BAP, which is itself bound to an avidin molecule that is associated to a membrane coupled biotin molecule. Figure 6 and its legend describes the outcome of a screen where a third component labelled "antigen" binds a member of a display system composed of two separate components, comprising a target molecule consisting of an antibody fused to a biotinylated BAP molecule which is bound to avidin itself associated to a cell surface coupled biotin.

18.1 Figure 6 represents the result of a display system of Figure 5 screened by an "antigen" or may be seen as a three component display system composed of an "antigen" binding to a target molecule consisting of an antibody fused to a biotinylated BAP molecule which is bound to avidin itself associated to a cell surface coupled biotin. First, there is no indication in document D2 that the antibody bound by an antigen illustrated in Figure 6 differs in each cell of the library of host cells. Second, the alternative three component display system illustrated in Figure 6 discloses an adapter molecule comprising a biotinylated BAP as a first binding site and an antibody binding site as second binding site which, because of its different varying binding affinities to the antigen, does not bind specifically to the display molecule in the sense of claim 1. Finally, the displayed antigen bound to the antibody does not comprise a modified polypeptide specifically selected from the group listed in claim 1 either.

18.2 The most promising embodiment in document D2 is the two separate component display system of Figure 5 consisting of a display molecule labelled as "protein" fused to an adapter molecule consisting of a biotinylated BAP, which is itself bound to an avidin

molecule that is associated to a membrane coupled biotin molecule. The expressed protein of interest (i.e. display molecule) is biotinylated in vivo and secreted to bind to the surface-located avidin. The engineered protein is a target antigen fused to a biotinylated biotin acceptor protein, which is not selected from the list of proteins of claim 1 and does not include a different modified polypeptide in each cell of the library to be screened for.

- 18.3 Starting from document D2, the problem to be solved can be defined as the provision of a modular surface display library to be queried/screened comprising a modified polypeptide selected from the list of claim 1 which does not have side reactions such as cell-cell interactions.
- 18.4 The solution proposed in claim 1 provides a three component system comprising a display molecule comprising a modified polypeptide available for screening which differs in each host cell. The display molecule comprising a modified molecule is anchored to a cell surface molecule by means of a polar adapter molecule.
- 18.5 The differences between the cell of Figure 5 of document D2 and of claim 1 is that the latter includes a polar adapter molecule and a modified molecule selected from the group consisting of a scaffold protein, a signal transduction protein, an antibody, an immunoglobulin, an immunoadhesin, a receptor, a ligand, an oncoprotein, a transcription factor, an enzyme and a fibronectin polypeptide, and that the polypeptide bound to the cell surface (i.e. the display molecule) in each host cell must be different.

- 18.6 As regards the argument that it would have been obvious to the skilled person starting from document D2 that the presented/exposed "Fc portion of antibodies" could be modified and that such Fc engineering was known at the priority date, the board notes that variation in the Fc portion is neither taught nor suggested nor an otherwise inevitable result of the disclosure of document D2.
- 18.7 It needs to be determined whether or not the skilled person, in the expectation of solving the above mentioned technical problem, would - instead of could - have modified the teaching in the closest prior art document so as to arrive at the claimed solution in an obvious way. Although a skilled person could have envisaged a library of host cells with the properties of claim 1, no convincing reasons on the basis of tangible evidence have been provided that would have prompted the skilled person to act in one way or the other. Appellant's objection appears therefore to be based on arguments involving hindsight.
- 18.8 In the absence of any pointer in document D2 which would have motivated the skilled person to design a library of host cells with the properties of claim 1, the board concludes that the claimed solution involves an inventive step. The same applies to claims 17 and 18.

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman:



L. Malécot-Grob

B. Stolz

Decision electronically authenticated