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Datasheet for the decision of 10 March 2023

Case Number: T 0293/22 - 3.3.08

Application Number: 14788445.6

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IPC: C40B10/00, C40B20/04, C40B40/02, C40B40/08

Language of the proceedings: EN

Title of invention:
Selection of Fab fragments using ribosomal display technology

Patent Proprietor:
Sutro Biopharma, Inc.

Opponent:
GeneFrontier Corporation

Headword:
Fab fragments/SUTRO BIOPHARMA

Relevant legal provisions:
EPC Art. 100(c), 111(1)
RPBA 2020 Art. 11, 12(2)

Keyword:
Grounds for opposition - added subject-matter (no)

Decisions cited:
T 1434/06, T 1205/13

Catchword:
-

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Case Number: T 0293/22 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 10 March 2023

Appellant: (Patent Proprietor)	Sutro Biopharma, Inc. 310 Utah Avenue, Suite 150 South San Francisco, California 94080 (US)
Representative:	Murgitroyd & Company Murgitroyd House 165-169 Scotland Street Glasgow G5 8PL (GB)
Respondent: (Opponent)	GeneFrontier Corporation Todai-Kashiwa Venture Plaza Rm No. 308 5-4-19, Kashiwa-no-Ha Kashiwa-shi Chiba 277-0882 (JP)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 6 December 2021 revoking European patent No. 2989239 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chair	T. Sommerfeld
Members:	B. Claes
	A. Bacchin

Summary of Facts and Submissions

I. The appeal lodged by the patent proprietor (appellant) lies from the opposition division's decision revoking European patent No. 2 989 239 (patent), entitled "*Selection of Fab fragments using ribosomal display technology*", granted on European patent application No. 14 788 445.6, which had been filed as an international application published as WO 2014/176327 (application as filed).

II. An opposition was filed against the patent, and the opposition proceedings were based on the grounds for opposition in Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and in Article 100(b) and 100(c) EPC.

III. In the decision under appeal, the opposition division held, *inter alia*, that Article 100(c) EPC prejudiced the maintenance of the patent as granted (main request) because claim 1 as granted extended beyond the content of the application as filed. The decision under appeal also dealt with 15 auxiliary requests.

IV. With the statement of grounds of appeal the appellant maintained all claim requests on which the decision under appeal was based and argued, *inter alia*, that claim 1 of the patent (main request) did not extend beyond the content of the application as filed.

V. The appellant's arguments can be summarised as follows.

The skilled person considering claim 1 as filed would have turned to the embodiments in the description

disclosing general teaching and would have construed them as elements which could be generally incorporated into the claimed method.

Paragraph [0098] taught that the presence of the variable light (V_L) chain assisted proper folding of the variable heavy (V_H) chain, and paragraph [0099] disclosed that V_L chain domains of the second library could be produced in a first reaction vessel and then added to a second reaction vessel in which ribosomal display was performed using the RNA of the first library of V_H chains. The skilled person would understand that the teaching in the last sentence of paragraph [0098] read into the teaching of paragraph [0099].

For the situation where separate reaction vessels were used, paragraph [0099] taught a clear order of the steps, which was also provided in paragraph [0014].

Examples 3 and 4 of the application as filed gave the skilled person pointers to a method in which generated (pre-purified) V_L chains were provided to the Fab HC library in a coupled transcription/translation reaction, which is different from the coexpression of the V_H and V_L chains.

VI. The appellant requests that the decision under appeal be set aside and
- that the claims of the main request or, alternatively, of one of auxiliary requests 1 to 15 be considered to meet the requirements of Article 123(2) and (3) EPC and
- that the case be remitted to the opposition division for further prosecution
Oral proceedings were requested "*in the event that the*

Board is minded to conclude that our Main Request is deemed to contravene the requirements of the EPC".

The respondent (opponent) has not made any submissions or formulated any requests in the appeal proceedings.

Reasons for the Decision

1. The appeal is admissible.

Decision in written proceedings

2. The appellant requests oral proceedings as an auxiliary measure in the event that the board is minded to conclude that the main request contravenes the requirements of the EPC. However, since the board finds that claim 1 of the patent as granted (main request) does not extend beyond the content of the application as filed (see point 14.) and thus grants the appellant's higher-ranking request for remittal to the opposition division for further prosecution, the present decision can be handed down in the written proceedings and no oral proceedings before the board need to be scheduled (Article 12(8) RPBA). Furthermore, the decision is based only on the arguments and evidence filed by the appellant with the statement of grounds of appeal and on the opposition division's decision (Article 113(1) EPC). Furthermore, the appellant is not adversely affected by the board's decision to remit the case to the opposition division for further prosecution as it is in line with the appellant's request (see Case Law of the Boards of Appeal of the European Patent Office, 10th edition 2022 ("CLBA"), III.C.4.5 and e.g. decisions T 1434/06, point 3, and T 1205/13, point 3).

The patent as granted (main request) - claim 1
Added subject-matter (Article 100(c) EPC)

3. Claims 1 and 2 of the application as filed read:

"1. A method for selecting a Fab fragment of interest from a library of Fab fragments comprising variable heavy (V_H) chain domains and variable light (V_L) chain domains, the method comprising:
i) generating a first library of DNA encoding V_H or V_L chain domains where the library comprises at least 10^2 different library members, each member having a different base sequence;
ii) generating a second library of between 1 and 20 variable chain domain members where the members are V_H chain domains when the first library is made up of DNA encoding V_L chain domains and the members are V_L chain domains when the first library is made up of DNA encoding V_H chain domains and where the members of the second library have different primary amino acid sequences;
iii) transcribing the first library of DNA to RNA;
iv) translating the RNA of the first library in a cell free protein synthesis system to generate a ribosomal display reaction system comprising a population of complexes comprising a strand of an RNA molecule, a ribosome and either V_H chain domains or V_L chain domains;
v) combining the population of complexes from the first library with the members of the second library to generate a library of Fab fragment members where library members comprise a complex comprising a V_H chain, in association with a V_L chain domain where one chain is associated with an RNA molecule and a ribosome; and

vi) selecting the Fab fragments of interest from the library of Fab fragments.

2. The method of claim 1, wherein the second library has only one member."

4. Claim 1 of the patent as granted reads (deletions as compared with claim 1 of the application as filed are struck-through and insertions as compared with claim 1 of the application as filed are underlined):

"1. A method for selecting a Fab fragment of interest from a library of Fab fragments comprising variable heavy (V_H) chain domains and variable light (V_L) chain domains, the method comprising:
i) generating a first library of DNA encoding V_H ~~or V_L~~ chain domains where the library comprises at least 10^2 different library members, each member having a different base sequence;
ii) generating a second library of ~~between 1 and 20 variable~~ one V_L chain domain member~~s where the members are V_H chain domains when the first library is made up of DNA encoding V_L chain domains and the members are V_L chain domains when the first library is made up of DNA encoding V_H chain domains and where the members of the second library have different primary amino acid sequences~~;
iii) transcribing the first library of DNA to RNA;
iv) translating the RNA of the first library in a cell free protein synthesis system to generate a ribosomal display reaction system comprising a population of complexes comprising a strand of an RNA molecule, a ribosome and ~~either~~ V_H chain domains~~ or V_L chain domains;~~
~~v) combining the population of complexes from the first library with the members of the second library~~ to

generate a library of Fab fragment members where library members comprise a complex comprising a V_H chain, in association with a V_L chain domain where ~~one~~ the V_H chain ~~the~~ is associated with an RNA molecule and a ribosome; wherein the step of translating the RNA of the first library and generation of the V_L chain domains of the second library occur separately such that the generated V_L chain domains of the second library are added to the step of translating the RNA of the first library; and
v~~i~~) selecting the Fab fragments of interest from the library of Fab fragments."

5. The opposition division held the claim to extend beyond the content of the application as filed because the application as originally filed did not provide a direct and unambiguous disclosure for the selection made in step (iv) in combination with the selections made in steps (i) and (ii) of claim 1 of the application as filed.

6. The board agrees with the appellant and the opposition division that claim 1 forms an appropriate starting point for assessing the content of the application as filed. The claimed method for selecting a Fab fragment of interest from a library of Fab fragments comprising variable heavy (V_H) chain domains and variable light (V_L) chain domains comprises the steps of generating V_H and V_L chain domain libraries. These two libraries of chain domains are generated in different ways, it being specified in the claim that when one chain library is produced one way, the other chain library is produced the other way (see step ii)). Thus, claim 1 of the application as filed generally defines two alternative options for producing the library of Fab fragments. Furthermore, whether the second library defined in

claim 2 of the application as filed is related to the V_L chain domains or the V_H chain domains is directly determined by the choice made in step ii) of claim 1.

7. Paragraphs [0009], [0014], [0098] and [0099] of the description of the application as filed read:

"[0009] In some embodiments, the second library has between 1 and 20 variable chains domain members, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 members. In some embodiments, the second library has only one member. In some embodiments, the second library has 96 members."

"[0014] In some embodiments, the step of translating the RNA of the first library and generation of the variable chains of the second library occur simultaneously in a single reaction vessel. In some embodiments, the step of translating the RNA of the first library and generation of the variable chains of the second library occurs separately such that the generated variable chains of the second library are added to the step of translating RNA of the first library."

"[0098] In some embodiments, steps of translating RNA of the first library and generating the variable chains of the second library are performed in a single reaction vessel. For instance, the translation of RNA encoding V_H variable chain domains can occur in the same reaction vessel as the generation of the V_L chain domains of the second library. Similarly, the translation of RNA encoding V_L variable chain domains can occur in the same reaction vessel as the generation of the V_H chain domains of the second library. Without being bound to any theory, it has been discovered that

the presence of the V_L chain assists proper folding of the V_H chain."

"[0099] In some embodiments, steps of translating RNA of the first library and generating the variable chains of the second library are performed in separate reaction vessels. For instance, V_L chain domains of the second library can be produced in a first reaction vessel, and then added to a second reaction vessel in which ribosomal display is performed using the RNA of first library of V_H chains." (emphasis added by the board)

8. The board considers that the skilled person would directly and unambiguously derive the subject-matter of claim 1 as granted from claim 1 as originally filed combined with the disclosures in claim 2 (see point 3.) and paragraph [0009], second sentence, paragraph [0014], last sentence, and paragraph [0099], last sentence (see emphasis added by the board in point 7. above).

9. Firstly, the last sentence of paragraph [0099] discloses the particular option for the embodiment disclosed in paragraph [0014], last sentence, whereby the step of translating the RNA of the first library (thus relating to V_H) and the generation of the variable chains of the second library (thus relating to V_L) occur separately, such that the generated variable chains of the second library (relating to V_L) are added to the step of translating RNA of the first library (relating to V_H). These two paragraphs thus explicitly disclose not only the option selected in the claim from the two options generally defined in claim 1 of the application as filed (see point 6.), but also the addition of the generated V_L chains of the second

library (proteins) to the step of translating RNA of the first library relating to V_H.

10. Secondly, the board considers that restricting the second library to only one V_L chain domain member (see step ii)) is disclosed in claim 2 as filed and paragraph [0009], second sentence, of the application as filed and is implicit for each of the two options generally defined in claim 1 of the application as filed (see also point6.). Therefore, the opposition division's concerns in point 3.3 of the decision under appeal, namely that the limitation of the second library to a single member in claim 2 is equally applicable to V_H and V_L libraries and that the claim does not provide that, when a single member forms the second library, it is the V_H mRNA first library that is complexed with the ribosome and the second V_L mRNA library is separately expressed and then added, are without merit.

11. Although the opposition division agreed that all the amendments in the claim were individually disclosed in the application as filed, it held that there was no direct and unambiguous disclosure of the combination of those features (see point 3. of the reasons of the decision under appeal). It further held that the application as filed was "*not a reservoir from which separate features from different embodiments* [could] *be combined*" and the description lacked "*any clear pointers*" to the specific combination in the amendment (see point 3.3 of the reasons of the decision under appeal).

12. However, as has been established in points 8. to 10. above, for a skilled person to directly and unambiguously derive the claimed subject-matter, they

merely have to refer to one of the two options generally defined in claims 1 and 2 of the application as filed and combine it with a particular set of embodiments that are disclosed in the description and directly functionally related to each other (disclosed in paragraphs [0014] and [0099]). This does not amount to the alleged combination of a selection of features from a "reservoir" of separate embodiments disclosed in the description of the application as filed. Under these circumstances, a pointer to the claimed combination is not necessary.

13. The board notes that it has come to its decision that the subject-matter is directly and unambiguously disclosed without referring to i) the disclosure in paragraph [0098], in particular the last sentence, and ii) examples 3 and 4 of the application as filed. Accordingly, the opposition division's concerns that paragraphs [0098] and [0099] of the application as filed related to two separate embodiments, that the final sentence of paragraph [0098] was not a general statement but only applicable to the embodiment in that paragraph, and that examples 3 and 4 related to embodiments in which the translation/generation reactions were carried out together and required the use of pre-purified V_L domain members (see points 3.1 and 3.2. of the decision under appeal, respectively) are not deemed pertinent for the board's decision.

14. On the basis of the above considerations, the board decides that the opposition division erred in deciding that claim 1 of the patent as granted (main request) extended beyond the content of the application as filed. Accordingly, the board does not need to deal with the auxiliary requests.

Remittal (Article 111(1) EPC and Article 11 RPBA)

15. Pursuant to Article 111(1) EPC, the board may either exercise any power within the competence of the department which was responsible for the decision under appeal or remit the case to that department for further prosecution. It is thus at the board's discretion whether it examines and decides on the case or whether it remits the case to the department which was responsible for the decision under appeal.

16. It is the primary function of appeal proceedings to give a judicial decision on the correctness of the decision under appeal (see Article 12(2) RPBA and CLBA, V.A.1.1, second paragraph and the decisions referred to in that chapter).

17. With respect to the main request, the opposition division took a reasoned decision only on the ground for opposition under Article 100(c) EPC (see point 5. above). Other grounds for opposition have not been examined yet. Not remitting the case to the opposition division would therefore require the board to carry out an in-depth examination of the opposition, rather than review the contested decision in a judicial manner, which is the primary purpose of appeal proceedings.

18. In view of these considerations, there are special reasons within the meaning of Article 11 RPBA for remitting the case to the opposition division for further prosecution and thus to grant the appellant's request to that effect.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division for further prosecution.

The Registrar: The Chair:

B. Brückner T. Sommerfeld

Decision electronically authenticated