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Datasheet for the decision of 16 May 2024

Case Number: T 1664/22 - 3.3.08

Application Number: 17194268.3

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Title of invention:
MIRAC PROTEINS

Applicant:
BioAtla, Inc.

Headword:
Mirac proteins/BIOATLA

Relevant legal provisions:
EPC Art. 56

Keyword:
Main request and auxiliary requests 1 to 3 - Inventive step (no)

Decisions cited:

Catchword:

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Case Number: T 1664/22 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 16 May 2024

Appellant: (Applicant)	BioAtla, Inc. 11085 Torreyana Road, Suite 100 San Diego, CA 92121 (US)
Representative:	Ogilvie-Emanuelson, C.M. De Vries & Metman Overschiestraat 180 1062 XK Amsterdam (NL)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 11 January 2022 refusing European patent application No. 17194268.3 pursuant to Article 97(2) EPC**

Composition of the Board:

Chair	T. Sommerfeld
Members:	D. Pilat
	R. Winkelhofer

Summary of Facts and Submissions

I. European patent application 17 194 268.3 was filed as a divisional application of the earlier European patent application No. 10 751 262.6 filed as international application and published as WO 2010/104821.

II. The examining division found the subject matter of the claims of the main request and of auxiliary requests 1 to 3 to lack clarity (Article 84 EPC) and the claims of auxiliary requests 4 to 7 to lack an inventive step (Article 56 EPC). The application was refused.

III. The applicant (appellant) lodged an appeal against the decision of the examining division.

IV. With the statement of grounds of appeal, they submitted a main request and first to third auxiliary requests.

V. The claims of the present main request and first to third auxiliary requests are identical to the claims of the main request and auxiliary requests 1, 4 and 5 of the decision under appeal, respectively.

VI. Claim 1 of the main request reads as follows:

"1. A method of preparing a conditionally active antibody, the method comprising steps of:

i. evolving a DNA which encodes a parent antibody using one or more evolutionary techniques to create mutant DNAs;

ii. expressing the mutant DNAs to obtain mutant antibodies including at least one mutant antibody which exhibits a decrease in an activity in an assay at a normal physiological pH, in comparison

to an activity of the parent antibody in the assay at the normal physiological pH; and an increase in an activity in an assay at an aberrant pH when compared to an activity of the parent antibody in the assay at the normal physiological pH; and

iii. selecting from the mutant antibodies the conditionally active antibody which exhibits:

a. a decrease in the activity in the assay at the normal physiological pH, in comparison to the activity of the parent antibody in the assay at the normal physiological pH;

b. an increase in the activity in the assay at the aberrant pH in comparison to the activity of the parent antibody in the assay at the aberrant pH; and

c. an increase in the activity in the assay at the aberrant pH when compared to the activity of the same mutant antibody in the assay at the normal physiological pH; and

wherein the normal physiological pH is a pH that is within a normal range of the physiological pH at a tissue or organ at a site of action and the aberrant pH is a pH that deviates from the normal physiological pH."

VII. In a communication under Article 15(1) RPBA, the board expressed a provisional opinion on Articles 84 and 56 EPC.

VIII. The following documents are referred to in this decision:

D1: WO 2004/035752 A2
D3: WO 03/105757 A2

IX. The appellant's submissions, insofar as they are relevant to the decision, are discussed in the Reasons for the Decision, below.

X. The appellant requests that the appealed decision be set aside and amended such that a patent be granted on the basis of the main request, or on the basis of the first to third auxiliary requests.

Reasons for the Decision

Main Request
Inventive step - claim 1

1. According to the patent, the invention "relates to a method of generating conditionally active biologic proteins from wild type proteins, in particular therapeutic proteins, and which are reversibly or irreversibly inactivated at the wild type normal physiological conditions" (paragraph [0002]). In particular, the claimed invention is directed at a method of preparing a pH-dependent conditionally active antibody that is able to preferentially deliver a desired level of activity to a treatment location in the body where an aberrant pH exists, in order to reduce side effects of the treatment.

2. Document D3, which is also concerned with providing therapeutic compounds that preferentially affect targeted cells and tissues in order to reduce side effects (document D3, page 1, lines 17 to 20, page 2, lines 12-16), is considered the closest prior art; this was also not disputed by the appellant. Document D3 specifically discloses screening procedures for mutant therapeutic antibodies which are selected for their

activity at aberrant pH versus normal pH (Example 1, page 63, lines 4 to 8).

3. While the examining division held that document D3 also disclosed selection criterion iii.a (appealed decision, point 26), in the appellant's favour it is assumed that the difference between the method described in document D3 and the method of claim 1 is that the claimed method comprises two additional selection criteria iii.a and iii.b, involving a comparison of the activity of the mutant antibodies with the activity of the parent antibody.

4. The technical effects linked to the distinguishing features are that:
- selecting mutant antibodies which have less activity than the parent antibody at the normal physiological pH (criterion iii.a) allows to reduce the side effects of the mutant antibody relative to the side effects of the parent antibody and
- selecting mutant antibodies which have a greater activity than the parent antibody at the aberrant pH (criterion iii.b) allows a reduction in the dose of the mutant antibody required to achieve the same level of activity as the parent antibody, thereby further reducing side effects.
In other words, the selection criterion iii.a of claim 1 prevents the selection of antibody expressing clones that have a higher activity at pH 7.4 than the parent antibody, avoiding thereby the selection of mutant antibodies that have increased side effects relative to the parent antibody, while the selection criterion iii.b of the claimed method enables a reduction in the dose of the mutant antibody required to achieve the same level of activity as the parent antibody, thereby further reducing side effects.

5. In contrast thereto, the method of preparing a conditionally active antibody described in document D3 comprises only selection criteria iii.c, i.e. the detection of an increase in the activity at the aberrant pH when compared to the activity of the same mutant antibody at the normal physiological pH. However, the aim of the screening method according to claim 1 comprising additional selection criteria iii.a and iii.b and the technical effect underlying them are still the same as in document D3, namely to reduce side effects while maintaining or increasing therapeutic activity of a conditionally active antibody; in other words, to improve the therapeutic window. The effect of the screening method of document D3 is thus not different from the technical effect achieved by the claimed screening method, possibly except in terms of degree.

6. Hence the objective technical problem can be seen as the provision of a further method of production and screening of conditionally active antibodies. Alternatively, and although there is no evidence on file for the alleged improvement over document D3, the technical problem can be seen, in agreement with the appellant, as the provision of a method to obtain a pH dependent conditionally active antibody that can preferentially deliver a certain level of activity to a treatment location in the body where an aberrant pH exists, in order to reduce side effects beyond the reduction in side effects that is achieved by the mutant antibodies selected by application of the selection criteria of document D3. This result must be achieved without compromising the efficacy of the antibody by maintaining the same level of binding activity as the parent antibody, so that the minimum

effective dose is maintained at the same level as the parent antibody.

7. Independently of which of the two technical problems the inventive-step analysis is based upon, the method according to claim 1 solves these problems across the whole scope of the claim.

8. It remains to be assessed whether or not the skilled person starting from the closest prior art method and faced with the problem(s) defined above, would have arrived at the method of claim 1 in an obvious manner.

9. It is within the normal tasks of a skilled person to further develop the existing state of the art by routine adaptations and use of known alternatives (cf. T 688/14 , point 25.1 of the Reasons). Comparing the activity of a mutant antibody to the activity of its parent antibody is an obvious screening step whenever mutagenesis is used in order to produce antibodies with increased or decreased activity in given conditions. Hence the skilled person, motivated to provide a further or improved production and screening method for conditionally active therapeutic antibodies, would just consider adding more screening steps, such as those of steps iii.a and iii.b of claim 1, and would arrive at the claimed invention without inventive skill.

10. It is true that, as argued by the appellant, none of the cited prior art suggests a method wherein the activity of the mutant antibody should be compared to the activity of the parent antibody, nor does it provide any reason to compare to the activity of the parent antibody in accordance with selection criteria iii.a and iii.b of claim 1. Nevertheless, the skilled person needs no indication or incentive to use

additional selection criteria, e.g. to add further screening steps, such as those of steps iii.a and iii.b, or any other screening steps related to antibody activity, for which no technical effect has been demonstrated, in order to provide a further or improved method for preparing conditionally active antibodies, by applying standard and more stringent optimization steps.

11. Claim 1 of the main request lacks inventive step (Article 56 EPC).

First auxiliary request

12. Claim 1 of the first auxiliary request differs from claim 1 of the main request by the addition of a further screening step iii.d which reads "a change in the activity from the activity at the normal physiological pH to the aberrant pH is reversible".

13. This additional selection criterion in a method of preparing a conditionally active antibody leads to the detection of particularly valuable therapeutic antibodies that are active when exposed to the aberrant pH, but will revert to their lower activity state when the therapeutic again encounters the normal physiological pH, thereby limiting the period of time that the antibody is active within the host (application as filed, paragraph [00100]). However, this additional feature is merely a further selection criterion for a screening step which is obvious to the skilled person seeking a process for the preparation of a conditionally active antibody having the given property. Such a selection step was known from document D1, which also teaches screening for reversible

activity of a therapeutic antibody (see Example 7 and Figs. 15A-15E).

14. It is true that the detection of the reversible activity in document D1 is carried out in the opposite direction than demanded by feature iii.d of claim 1 which requires that a change in the activity from the activity at the normal physiological pH to the aberrant pH is reversible, and not that the change from the aberrant pH to the normal physiological pH is reversible. However, the selection of step iii.d of claim 1 does not require a change in activity to be measured in one specific direction, as the change is reversible. The notion that a pH dependent change is "reversible" implies that it is bidirectional. Any understanding of this term that a change measured in one direction cannot be produced in the opposite direction is flawed, as it would mean that the change is direction-dependent and therefore "irreversible". Furthermore, there is no minimum level in the change of activity set out in claim 1.

15. Claim 1 of the first auxiliary request also lacks an inventive step (Article 56 EPC).

Second auxiliary request

16. Claim 1 of the second auxiliary request differs from claim 1 of the main request by replacement of the word "preparing" in the preamble by "selecting".

17. Since the amendment in the second auxiliary request was introduced to overcome a clarity objection, and the appellant has not even argued that the new feature was associated with a technical effect, the same conclusion

on lack of inventive step as above for the main request and the first auxiliary request applies.

Third auxiliary request

18. Claim 1 of the third auxiliary request comprises the amendments of both the first and second auxiliary requests.

19. Since none of the amendments introduced in claim 1 of the first and second auxiliary requests are associated with a technical effect, individually or in combination, the conclusion on lack of inventive step as above for the first and second auxiliary request applies to the third auxiliary request as well.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

A. Vottner T. Sommerfeld

Decision electronically authenticated