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Datasheet for the decision of 21 June 2022

Case Number: T 1612/16 - 3.3.04

Application Number: 09170230.8

Publication Number: 2157192

IPC: C12Q1/68

Language of the proceedings: EN

Title of invention:
Compositions for diagnosis and therapy of diseases associated with aberrant expression of futrins (R-Spondins)

Patent Proprietor:
Deutsches Krebsforschungszentrum

Opponent:
OncoMed Pharmaceuticals, Inc.

Headword:
Anti-Futrin 2 antibodies/ONCOMED PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 56, 76(1), 83

Keyword:
Main and auxiliary requests I to VI - subject-matter extends beyond content of earlier application (yes)
Inventive step - auxiliary request VII (yes)
Sufficiency of disclosure - auxiliary request VII (yes)

Decisions cited:
T 0609/02

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

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Case Number: T 1612/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 21 June 2022

Appellant: (Opponent)	OncoMed Pharmaceuticals, Inc. 800 Chesapeake Drive Redwood City, CA 94063 (US)
Representative:	Mathys & Squire The Shard 32 London Bridge Street London SE1 9SG (GB)
Respondent: (Patent Proprietor)	Deutsches Krebsforschungszentrum Im Neuenheimer Feld 280 69120 Heidelberg (DE)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstraße 3 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 April 2016 concerning maintenance of the European Patent No. 2157192 in amended form**

Composition of the Board:

Chair	B. Claes
Members:	A. Chakravarty
	M. Blasi

Summary of Facts and Submissions

I. By interlocutory decision, the opposition division decided that European patent No. 2 157 192, entitled "*Compositions for diagnosis and therapy of diseases associated with aberrant expression of futrins (R-Spondins)*", as amended in the form of the main request, met the requirements of the EPC.

II. The patent was granted on European patent application No. 09 170 230.8, which is a divisional application of earlier European application No. 04 765 894.3. This earlier application was filed as an international application, published as WO 2005/040418 (the earlier or parent application). It is noted that the description of the application is identical with the description of earlier application and further comprises the claims of the earlier application as preferred embodiments, thus a reference to a page or paragraph in either is applicable to both. The claims of the application and the earlier application differ.

III. In the decision under appeal, the opposition division dismissed objections raised by the opponent under Article 100(a),(b) and (c) EPC.

IV. The opponent (appellant) filed an appeal against the interlocutory decision of the opposition division. The patent proprietor is respondent to this appeal.

V. The respondent replied to the appellant's statement of grounds of appeal. It maintained as a main request the version of the patent considered allowable by the opposition division. It also submitted sets of claims of auxiliary requests I to VII.

VI. Claim 1 of the main request reads:

"1. Use of a ligand which specifically binds to a Futrin 2 polypeptide according to SEQ ID NO: 27 for the preparation of a pharmaceutical composition for inhibiting the Wnt signal cascade, wherein the ligand is an antibody".

Claim 1 of auxiliary request I differs from claim 1 of the main request in that the expression "Wnt signal cascade", used in claim 1 of the main request, is replaced by "Wnt/β-catenin signal cascade".

Claim 1 of auxiliary request II is identical to claim 1 of the main request.

Claim 1 of auxiliary request III differs from claim 1 of the main request in that it refers to a pharmaceutical composition for the treatment of tumours.

Claim 1 of auxiliary request IV is a combination of the features of claim 1 of auxiliary requests I and III.

Claim 1 of auxiliary request V differs from claim 1 of the main request in that the expression "associated with aberrant expression of the gene encoding Futrin 2" is inserted after the word "tumors".

Claim 1 of auxiliary request VI differs from claim 1 of auxiliary request V in that it additionally refers the "Wnt/β-catenin signal cascade" instead of the "Wnt signal cascade".

Auxiliary request VII corresponds to the main request with claims 1 to 4 deleted.

Auxiliary request VII has six claims of which claims 1 and 2 are independent. Independent claims 1 and 2 read:

"1. A method for identifying activators/agonists or inhibitors/antagonists of a Futrin 2 polypeptide according to SEQ ID NO: 27 or a polypeptide showing an identity of at least 80% thereto comprising the steps of:

(a) incubating a candidate compound with said polypeptide;

(b) assaying the biological activity of Futrin 2 according to SEQ ID NO: 27 or a polypeptide showing an identity of at least 80% thereto, in a Wnt inducible luciferase reporter assay in transfected HEK 293 cells, and

(c) determining if the biological activity of said polypeptide has been altered.

2. A method for identifying and obtaining a drug candidate for therapy of a disease associated with aberrant activities of Futrin 2 according to SEQ ID NO: 27 or a polypeptide showing an identity of at least 80% thereto comprising the steps of:
(a) contacting a Futrin 2 polypeptide according to SEQ ID NO: 27 or a polypeptide showing an identity of at least 80% thereto or a cell expressing said polypeptide, and optionally the corresponding ligand(s), in the presence of components capable of providing a detectable signal in response to binding to said drug candidate to be screened; and
(b) detecting presence or absence of a signal or increase of the signal generated, wherein the presence or increase of the signal is indicative for a putative

drug, wherein the activity of Futrin 2 according to SEQ ID NO: 27 or a polypeptide showing an identity of at least 80% thereto is analysed by a Wnt-inducible luciferase reporter assay in transfected HEK 293 cells".

Claims 3 to 6 depend on claim 1 and/or claim 2.

VII. The board issued a summons to oral proceedings as requested by the parties and subsequently issued a communication under Article 15(1) RPBA on 16 February 2021, setting out its preliminary opinion on some of the issues in the case. It informed the parties that it was in preliminary agreement with the appellant that the parent application as filed did not disclose the use of an anti-Futrin 2 antibody for the preparation of a pharmaceutical composition for inhibiting the Wnt signal cascade and that this objection appeared to apply equally to the subject-matter of dependent claims 2 to 4 and to the subject-matter of claim 1 of auxiliary requests I to VI. With respect to the set of claims of auxiliary request VII it stated that its preliminary negative finding of added subject-matter did not appear to apply to this claim request.

VIII. Both parties informed the board in writing that they would not attend the oral proceedings. In its letter, dated 2 November 2021, the appellant also withdrew its request for oral proceedings, while the respondent, in its letter, requested that "*a decision be made on the basis of the corresponding evidence on file*". The board subsequently cancelled the oral proceedings.

IX. The following documents are mentioned in this decision.

D3: Goldblum S. *et al.*, Mol. Biol. Cell, 10 (1999), pages 1537-1551.

D6: Wu W. *et al.*, Current Biology, 10(24) (2000), pages 1611 -1614.

D12: WO 01/77169.

X. The submissions of the appellant as understood by the board are as follows:

Main request and auxiliary request I to VI
Claims 1 and 2 - Amendments (Article 76(1) EPC)

The earlier application was based on data allegedly showing that Futrins can be regarded as Wnt/β-catenin signalling modulators. However, there was no individualised disclosure of Futrin 2 as being of any particular interest and the disclosure of therapeutic antagonists was only at a general level, but with no individualisation of an antagonist antibody.

The first full paragraph on page 16 of the earlier application stated "*Preferably, the ligand is an antibody*". However, in context (see pages 13 to 15 of the earlier application) it was apparent that this passage related only to a diagnostic composition.

Auxiliary request VII - Claims 1 and 2
Inventive step (Article 56 EPC)

Objections regarding the subject-matter claimed in auxiliary request VII were maintained by reference to the notice of opposition.

In said notice of opposition, two lines of argument on inventive step were pursued.

i) Lack of inventive step over the disclosure of document D3 in combination with that in document D6.

According to the patent, the assay mentioned in these claims had been known at the relevant date, see e.g. document D6. From the disclosure in document D3 it was apparent that the relationship between thrombospondins and the Wnt/β-catenin signaling pathway was known to the skilled person. The skilled person also knew that the Wnt/β-catenin signaling pathway had an effect on the actin cytoskeleton and on endothelial barrier functions. Thus, the skilled person in search of an activator/agonist or a drug candidate for modulating said process would have immediately referred to document D6, which disclosed a Wnt-inducible luciferase reporter assay in transfected HEK 293 cells for the identification of potential inhibitors of the Wnt signal cascade. A combination of the disclosure in documents D3 and D6 would have led the skilled person to the claimed subject-matter.

ii) Lack of inventive step over the disclosure in document D12

Document D12 concerned screening chemical compounds using various polypeptides and a variety of drug screening techniques. The polypeptides used included SEQ ID NO: 34 which was the same Futrin 2 (SEQ ID NO: 27 in the patent). Document D12 further disclosed methods for detecting the specific binding of a polypeptide, e.g., a ligand or a receptor. The claimed methods were standard assays which allegedly derived their non-obviousness from the relationship between

Futrin 2 and Wnt. However, this relationship was also known from document D12. Thus, the subject-matter of claims 11 and 12 lacked an inventive step.

Disclosure of the invention (Article 83 EPC)
Claim 6

The claim referred to the screening method of claim 2, and specified the disease to be a tumor or a disease of the kidneys, muscles, bones and eyes. The claimed subject-matter relating to these diseases was not sufficiently disclosed. These were no more than a vague indication in the patent of a possible medical use. According to decision T 609/02 vague indication of a possible medical use for a chemical compound yet to be identified was a fundamentally insufficient disclosure.

XI. The submissions of the respondent as understood by the board are as follows:

Main request and auxiliary request I to VI
Claims 1 and 2 - Amendments (Article 76(1) EPC)

The opposition division had correctly rejected that selection from several lists was required to arrive at the claimed subject-matter. Arguments to this effect ignored the case law that the application should be interpreted by a skilled person with a mind willing to understand.

The skilled person could directly and unambiguously derive the claimed subject-matter from the disclosure in the earlier application. The title at the top of page 1 of this application (WO 2005/040419) already indicated that the invention related, *inter alia*, to

"*compositions for [...] therapy of diseases associated with aberrant expression of Futrins (R-Spondins)*".In line with this, the very first paragraph of the application, in the last sentence, disclosed that the invention related to pharmaceutical compositions containing a compound capable of modifying the activity of e.g. Futrin 2.

The activity of Futrin 2 was demonstrated in the Examples (i.e. its capacity to stimulate Wnt/β-catenin signalling and the possibility to reduce Wnt/β-catenin signalling by suppressing the expression of Futrin 2) and was explicitly addressed, e.g., on page 4, lines 1 to 6 of the earlier application:

"*In the present invention the following is shown for the first time: 1) Futrins enhance Wnt signaling and this is of physiological relevance since inhibition of Futrin 1 or 2 results in inhibition of the Wnt signal cascade (Wnt/β-catenin signaling). These data show that Futrins can be regarded as Wnt modulators*".

On page 20, second paragraph the (earlier) application disclosed that Futrin 2 could be used to screen for proteins or other compounds that bind to it and "*inhibit (antagonist) [---] activity*" of Futrin 2. Antibodies were explicitly mentioned as an example for such antagonist molecules. On page 20, third paragraph to page 25, first paragraph, the earlier application described how such a screening might be carried out. Thus, the screening for antagonists of Futrin 2, including the option that such an antagonist may be an antibody was explicitly disclosed. This disclosure was supplemented at the end of page 24, which made explicit reference to antagonistic antibodies and parts derived therefrom. Moreover, page 16, paragraph 2, provided a

generally applicable definition of the term "antibody" from which it could directly and unambiguously be derived that the antibodies specifically recognised Futrin 2.

XII. The requests of the appellant, as understood by the board and relevant for the decision, are that the decision under appeal be set aside and that the patent be revoked in its entirety.

XIII. The requests of the respondent, as understood by the board and relevant for the decision, are that the appeal be dismissed, or alternatively, that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the set of claims of one of auxiliary requests I to VII as filed with the reply to the appeal.

Reasons for the Decision

Main request - claim 1

Amendments (Article 76(1) EPC)

1. It is disputed between the parties whether nor not the earlier (parent) application explicitly or implicitly, directly and unambiguously discloses the use of an anti-Futrin 2 antibody for the preparation of a pharmaceutical composition for inhibiting the Wnt signal cascade, as claimed, to the skilled person using common general knowledge, and seen objectively and relative to the date of filing.

2. Both the opposition division and the respondent considered that page 16, second paragraph of the earlier application provide a basis for the use of an

anti-Futrin 2 antibody for the preparation of a pharmaceutical composition for inhibiting the Wnt signal cascade.

3. While the passage cited above does relate to anti-Futrin 2 antibodies, it does not disclose the use of these antibodies for the preparation of a pharmaceutical composition. The section to which the cited passage belongs is part of the definition of "*a diagnostic composition*" (see the paragraph bridging pages 13 and 14) where under definition (f), the composition may comprise "*at least one ligand capable of specifically binding to the molecule of* [(a) to (e)]". Anti-Futrin 2 antibodies (see page 16, first full paragraph) are disclosed as part of an explanation of the "*ligand*" which may be part of the aforementioned diagnostic composition (see page 15, final paragraph).

4. No other passages in the earlier application disclose the use of an antibody for the preparation of a pharmaceutical composition. The most pertinent disclosure in the earlier application that mentions pharmaceutical compositions is the paragraph bridging pages 30 and 31. This paragraph reads: "*Accordingly, the present invention also relates to a pharmaceutical composition comprising a nucleic acid molecule encoding a Futrin 1, 2, 3 and/or 4 polypeptide, a Futrin 1, 2, 3 and/or 4 polypeptide itself, recombinant vector (for examples, see below), antibody, activator/agonist, inhibitor/antagonist and/or binding partner of a Futrin 1, 2, 3 and/or 4 polypeptide and a pharmaceutically acceptable excipient, diluent or carrier*".

5. However, the target of the antibody is not defined in this paragraph nor is it disclosed that the antibody can inhibit the Wnt signal cascade. The claimed

subject-matter is not derivable from the above-mentioned paragraph in combination with the disclosure on page 15 either since, as noted above, the antibodies mentioned on that page are disclosed as being for use in a diagnostic composition.

6. The third full paragraph on page 34 of the earlier application states "*the use of a nucleotide molecule encoding a polypeptide having a biological activity of Futrin 1, 2, 3 and/or 4, a Futrin 1, 2, 3 and/or 4 polypeptide, an activator/agonist of a Futrin 1, 2, 3 and/or 4 polypeptide or binding partner of said polypeptide(s) for the preparation of a pharmaceutical composition for inhibiting the Wnt signal cascade which might be useful for supporting regenerative processes in a patient, e. g. growth of tissue like muscle, bone, hair, etc*".

7. This paragraph relates to the use of a nucleotide molecule for the preparation of a pharmaceutical composition but not to the use of an antibody for this purpose and is therefore not a disclosure of the claimed subject-matter.

8. In view of the above considerations, the skilled person cannot derive the claimed subject-matter directly and unambiguously from the earlier application. Thus, claim 1 of the main request does not meet the requirements of Article 76(1) EPC.

Auxiliary requests I to VI

Claim 1

9. Claim 1 of each of these auxiliary requests is, like claim 1 of the main request, also for the use of an

anti-Futrin 2 antibody for the preparation of a pharmaceutical composition. The above considerations on claim 1 of the main request (points 3. to 8.) therefore apply equally to the subject-matter of these claims, which therefore do not meet the requirements of Article 76(1) EPC.

Auxiliary request VII

10. In its response to the respondent's reply (which included the sets of claims of all auxiliary requests), the appellant made no objections under Article 76(1) EPC and/or Article 123(2) EPC to this claim request. The appellant however stated that it maintained "*all previously raised objections regarding the subject-matter in AR7*". Specifically maintained were the objections under Article 56 EPC raised in the notice of opposition dated 28 May 2014 regarding independent claims 11 and 12 as granted (corresponding to claims 1 and 2 of auxiliary request VII) and claims 13 to 16 as granted (corresponding to claims 3 to 6 of auxiliary request VII, see section VI., above). Also maintained were objections under Article 83 EPC against claim 16 as granted (corresponding to claim 6 of auxiliary request VII), and as claim 6 is a dependent claim, the same objections applied to claims 1 to 5 encompassing this subject-matter.

11. From these submissions, it is clear that the appellant objects to inventive step of the subject-matter of claims 1 and 2 for the reasons set out in the notice of opposition dealing with the issue of lack of inventive step in relation to claims 11 and 12 as granted, i.e. the submissions set out in the notice of opposition in section 8.2 entitled "Independent claims 11 and 12 lack inventive step over D3 and D6" and section 8.3 entitled

"Independent claims 11 and 12 lack inventive step over D12". In a similar manner, for lack of inventive step of the subject-matter of claims 3 to 6, the submissions in the notice of opposition dealing with inventive step of the subject-matter of claims 13 to 15, i.e. section 9.3, and of claim 16, i.e. section 9.4, are relied upon. Furthermore, it is clear that the invention defined in claims 1 to 6 is objected to under Article 83 EPC for the reasons set out in relation to claim 16 as granted, hence the last paragraphs of section 5.5. entitled *"The alleged indications in claims 8, 9 and 16 are not sufficiently disclosed (Art 83 EPC)*".

12. However, in relation to the statement that the appellant maintained "*all previously raised objections regarding the subject-matter claimed in AR7*", the board is at a loss to know which objections these could be or when they were raised. It is for a party to present its case in a clear and concise manner and not for the board to speculate what could have been intended, nor may the board make a party's case for it.

13. In view of the above considerations, the board has not taken into account objections except were the appellant's letter of 22 December 2017 identifies the objections relied on. Thus, the board has only considered the objections to claim 1 and 2 under Article 56 EPC raised in section 8.1 and 8.2 of the notice of opposition and the objections to claim 6 under Article 83 EPC set out in section 5.5. of the notice of opposition and those in sections 9.3 and 9.4 under Article 56 EPC for claims 3 to 6.

Claim 1 to 6 - inventive step (Article 56 EPC)

14. The objections raised in the notice of opposition were that the skilled person knew from document D3 that there was a relationship between thrombospondins and the Wnt/β-catenin signaling pathway which had an effect on the actin cytoskeleton and on endothelial barrier functions. The "*skilled person would, in search of an activator/agonist or a drug candidate that modulates said process* [the Wnt/β-catenin signaling pathway], *immediately refer to D6, which discloses a Wnt-inducible luciferase reporter assay in transfected HEK 293 cells for the identification of potential inhibitors of the Wnt signal cascade*". The combination of the disclosures in document D3 and D6 would have led the skilled person to the claimed subject-matter.

15. The appellant has however not explained why the skilled person would turn to the disclosure in document D3 (entitled "*Thrombospondin-1 Induces Tyrosine Phosphorylation of Adherens Junction Proteins and Regulates an Endothelial Paracellular Pathway*") concerning thrombospondin-1 when seeking to modulate the effects of Futrin 2. In the absence of such an explanation, the board cannot conclude that the disclosure in document D3, regardless of which disclosure in another document it is combined with, would have led the skilled person to the claimed invention.

16. In the notice of opposition, the appellant pursued a separate line of argument of lack of inventive step based on the disclosure in document D12. However, the appellant has merely alleged that document D12 discloses the relationship between Futrin 2 and Wnt, but has made no reference to any particular passages in

document D12 to support this argument. In such a situation, the board cannot find the line of reasoning convincing.

17. Thus, the board has seen no arguments that would convince it that the subject-matter of claims 1 to 6 does not meet the requirements of Article 56 EPC.

Claims 1 to 5 - disclosure of the invention (Article 83 EPC)

18. The appellant maintained the objections raised in section 5.5 of the notice of opposition. However, here the board can identify no more than an unsubstantiated allegation that the method of claim 16 as granted was insufficiently disclosed as far as the diseases in mentioned in the claim were concerned. The board is not persuaded by this line of argument as no convincing case has been made that the skilled person cannot carry out the method as claimed. It is also noted that the claimed subject-matter is not a medical use and thus the findings in decision T 609/02 cited by the appellant, are not relevant to the case.

19. In summary, the board is not convinced by the appellant's arguments of lack of inventive step or of lack of sufficient disclosure, set out in the notice of opposition in the sections relied upon. Thus, the set of claims of auxiliary request VII meets the requirements of the EPC.

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 with the order to maintain the patent in amended form with the following claims and a description and drawings to be adapted thereto:

claims 1 to 6 of auxiliary request VII filed with the reply to the statement of grounds of appeal.

The Registrar: The Chair:

I. Aperribay B. Claes

Decision electronically authenticated