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**Datasheet for the decision
of 12 June 2018**

Case Number: T 0511/14 - 3.3.04

Application Number: 08725133.6

Publication Number: 2121755

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A61P19/00

Language of the proceedings: EN

Title of invention:
Antibodies Specific for Dkk-1

Applicant:
MedImmune Limited

Headword:
DKK-1 antibodies/MEDIMMUNE

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - main and auxiliary request (no)

Decisions cited:

Catchword:



Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0511/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 12 June 2018

Appellant: MedImmune Limited
(Applicant) Milstein Building
Granta Park
Cambridge
CB21 6GH (GB)

Representative: AstraZeneca
Milstein Building
Granta Park
Cambridge CB21 6GH (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted on 24 October 2013 refusing European patent application No. 08725133.6 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: A. Chakravarty
L. Bühler

Summary of Facts and Submissions

- I. Appeal lies against the decision of the examining division to refuse European patent application EP 08 725 133.6, entitled "*Antibodies Specific for Dkk-1*". The application was filed as an international patent application, published as WO 2008/097510.
- II. The examining division considered a main and an auxiliary request. It held *inter alia* that the subject-matter of claims 1 to 20 of the main request lacked an inventive step (Article 56 EPC) and moreover, that the subject-matter of the auxiliary request lacked inventive step for the same reasons as that of the main request.
- III. The examining division, *inter alia*, held that no surprising technical effect could be acknowledged for the antibody RH2-18 over the antibody of the closest prior art disclosed in document D1 (WO 2006/015373) and thus the problem to be solved was the "*provision of alternative antibodies specific for Dkk-1*" and that the provision of the antibodies specifically defined in claim 1 was obvious for the following reasons:
- "Dkk-1 was known in the art [...] and both polyclonal and monoclonal antibodies specific for this protein had already been obtained, [as disclosed in several prior art documents [...]]. The skilled person, in light of these teachings, would consider obvious obtaining further Dkk-1 antibodies in order to solve the above stated problem, without the exercise of inventive skill. [...]. It follows that in the absence of any surprising technical effect, the claimed antibodies are considered arbitrary selections [...]." (see point 1.2.1, penultimate paragraph).*

IV. *"An additional objection of lack of inventive step" was raised by the examining division to those antibodies as claimed "comprising CDR sequences or VH or VL sequences having at least 80% or 90% sequence identity to certain defined sequences (those of the antibody RH2-18)". The reasoning was as follows:*

"These antibodies are defined partial structural elements and their sequences allow for less than 100% identity. Thus, in the hypothetical case that fully defined antibody RH2-18 would be proven superior to the antibodies of the prior art, then the problem to be solved would be the provision of improved Dkk-1 antibodies. In that case antibodies comprising some structural elements of said (fully defined) antibody [...] would not necessarily have said (potentially) surprising property and would not solve the problem of providing improved anti-Dkk-1 antibodies. [...]. In the present case the problem would be reformulated to the provision of alternative (instead of improved) antibodies specific for Dkk-1. The solution, as already discussed for the fully defined antibody RH2-18, would not be considered inventive" (see point 1.2.1, final paragraph).

V. With the statement of grounds of appeal, the appellant submitted sets of claims of a main request and an auxiliary request, both *"corresponding"* to the main request and auxiliary request considered by the examining division. In relation to inventive step, arguments were provided as to why the antibody RH2-18 had superior properties over the antibody of the prior art. No arguments were provided with regard to the *"additional objection of lack of inventive step"* of the examining division as set out in section IV above.

VI. Claim 1 of the main request reads:

"1. An isolated antibody or immunologically functional fragment thereof, comprising:
(a) light chain (LC) complementary determining regions (CDRS) comprising
(i) an LC CDR1 with at least 80% sequence identity to SEQ ID NO: 12,
(ii) an LC CDR2 with at least 80% sequence identity to SEQ ID NO: 13, and
(iii) an LC CDR3 with at least 80% sequence identity to SEQ ID NO: 14; and
(b) one or more heavy chain (HC) CDRs comprising
(i) an HC CDR1 with at least 80% sequence identity to SEQ ID NO:9,
(ii) an HC CDR2 with at least 80% sequence identity to SEQ ID NO: 10, and
(iii) an HC CDR3 with at least 80% sequence identity to SEQ ID NO: 11;

wherein the antibody or immunologically functional fragment thereof can specifically bind a Dkk-1 polypeptide".

Claim 1 of the auxiliary request reads:

"1. An isolated antibody or immunologically functional fragment thereof, comprising:
(a) light chain (LC) complementary determining regions (CDRS) comprising
(i) an LC CDR1 with the sequence as set forth in SEQ ID NO: 12,
(ii) an LC CDR2 with the sequence as set forth in SEQ ID NO: 13, and
(iii) an LC CDR3 with the sequence as set forth in SEQ ID NO: 14; and

- (b) one or more heavy chain (HC) CDRs comprising
 - (i) an HC CDR1 with the sequence as set forth in SEQ ID NO:9,
 - (ii) an HC CDR2 with the sequence as set forth in SEQ ID NO: 10, and
 - (iii) an HC CDR3 with the sequence as set forth in SEQ ID NO: 11".

VII. The appellant's arguments on inventive step can be summarised as follows:

The examining division considered document D1 to represent the closest prior art, disclosing anti-Dkk-1 antibodies (in particular antibody 11H10, example 5) and their use to treat arthritis, diseases responsive to stem cell renewal, inflammatory, neurological, ocular, renal, pulmonary, bone and skin diseases. Also disclosed were methods to stimulate bone growth using said antibodies.

Tests carried out with antibody RH2-18 of the present invention demonstrated that it had superior properties over antibody 11H10 of document D1. Example 5 of document D1 described the *in vivo* testing of 11H10 in ovariectomized mice. The effect on lumbar bone mineral density (BMD) was measured compared to baseline and parathyroid hormone (PTH) administered at 100µg/kg as a positive control. The results, in Figure 3B, showed that a similar effect as for PTH was found only for a dose of 10 mg/kg twice per week of 11H10 at day 28. Only modest, or small, differences from baseline were found for doses of 3mg/kg and 30mg/kg.

By contrast, in a similar study, RH2-18 was found, at 56 days, to have the same or greater effect than PTH at a concentration of only 1mg/kg. This increase in

activity by an order of magnitude could not have been predicted from document D1.

It was accepted that the experiments in document D1 and the present application were not carried out under identical conditions but since there was no other data, the examining division should have considered whether the data presented met the required standard of proof. It was not acceptable to reject it, simply because the conditions used in the two experiments were not identical.

Both experiments were carried out on ovariectomized mice and both included PTH as positive control. Moreover, both experiments compared effects on lumbar vertebrae. The main difference between them lay in the time point at which measurements were taken, which did not affect the conditions under which the experiments were performed. The later time point at which the measurements for antibody RH2-18 were made rather indicated that it had an even greater effect. Thus, conditions used in the experiments were sufficiently similar to allow the conclusion that antibody RH2-18 was more effective than antibody 11H10.

- VIII. The board appointed oral proceedings and subsequently issued a communication pursuant to Article 15(1) RPBA in which it informed the appellant of its preliminary opinion on the appeal. In this communication it was, *inter alia*, stated that even if the RH2-18 antibody were accepted as having demonstrably superior properties to the 11H10 antibody disclosed in document D1, these would only be plausibly demonstrated for the particular embodiment of the RH2-18 antibody itself (see point 7 of the communication).

- IX. Oral proceedings were held on 12 June 2018. The appellant did not appear. Accordingly, the oral proceedings were held in the absence of the appellant.
- X. The appellant requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request, or, alternatively, on the basis of the claims of the auxiliary request, both filed with the statement of grounds of appeal.

Reasons for the Decision

1. The appellant, although duly summoned, did not attend the oral proceedings. Pursuant to Rule 115(2) EPC, the proceedings were continued in the absence of the appellant who was treated as relying only on the written case (Article 15(3) RPBA).

Main and auxiliary request - claim 1 *Article 56 EPC - Inventive step*

2. The subject-matter of claim 1 of both the main and auxiliary request is an isolated antibody or immunologically functional fragment thereof which can specifically bind a Dkk-1 polypeptide. The antibody (or fragment) is further defined by the amino acid sequence of three CDRs of the light chain and (at least) one of three CDRs of the heavy chain. An embodiment of claim 1 of both requests is an antibody in which CDRs 1 to 3 of the light chain are represented by SEQ ID NOs: 12 to 14, respectively and the one of CDRs 1 to 3 of the heavy chain is represented by one of SEQ ID NOs: 9 to 11, while the remaining two CDRs may have any sequence.

3. In the decision under appeal, the examining division held, *inter alia*, that embodiments of claim 1 which differed from the exemplified antibody RH2-18 in that they did not possess a full complement of 6 CDRs "*would not necessarily have said surprising property and would not solve the problem of providing improved anti-Dkk-1 antibodies*" and that these antibodies only solved the problem of provision of alternative antibodies specific for Dkk-1. Anti-Dkk1-1 antibodies were known to the skilled person, for example the antibody 11H10 disclosed in document D1, and the skilled person also how to obtain further antibodies with the same specificity. The claimed antibodies represented an obvious solution to the problem of providing alternative antibodies specific for Dkk-1 because they represented arbitrary selections from the all possible solutions. The claimed subject-matter therefore lacked an inventive step (see section IV, above).
4. The appellant provided no arguments as to why this finding of the examining division was wrong. The board considers that, even if the RH2-18 antibody were accepted as having demonstrably superior properties compared to antibody 11H10 disclosed in document D1, representing the closest prior art, these properties are only demonstrated for the particular embodiment of the RH2-18 antibody itself. This is because the structural reason for said superior properties is not disclosed in the application or otherwise known. It therefore cannot be inferred that any favourable properties of the RH2-18 antibody are inevitably also properties of every embodiment of the claimed subject-matter.
5. The board therefore sees no reason to come to a conclusion different to the one reached by the

examining division. The subject-matter of claim 1 of both the main and auxiliary request therefore does not fulfil the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated