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**Datasheet for the decision
of 27 April 2010**

Case Number: T 1902/07 - 3.3.04

Application Number: 97939609.0

Publication Number: 0961613

IPC: A61K 31/45

Language of the proceedings: EN

Title of invention:

Methods and compositions for the treatment of bone resorption disorders, including osteoporosis

Applicants:

MOUNT SINAI SCHOOL OF MEDICINE et al.

Headword:

Treatment of osteoporosis/MOUNT SINAI S.M.

Relevant legal provisions:

EPC Art. 56

Keyword:

"Main request and auxiliary request: inventive step (no)"

Decisions cited:

-

Catchword:

-



Case Number: T 1902/07 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 27 April 2010

Appellants:

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Decision under appeal:

**Decision of the Examining Division of the
European Patent Office posted 23 May 2007
refusing European application No. 97939609.0
pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: R. Gramaglia
M. Wieser

Summary of Facts and Submissions

I. The appellants (applicants) lodged an appeal against the decision of the examining division on the refusal under Article 97(1) EPC 1973 of the European patent application No. 97 939 609.0 (published as WO-A-98/08494), having the title "Methods and compositions for the treatment of bone resorption disorders, including osteoporosis".

II. The decision was based on claims 1 to 11 filed with the letter dated 12 December 2005, of which independent claims 1 and 6 read as follows:

"1. Use of a compound which specifically inhibits cathepsin K activity of an osteoclast for the manufacture of a medicament for ameliorating bone resorption disorder symptoms".

"6. Use of a compound which specifically inhibits cathepsin K activity of a macrophage for the manufacture of a medicament for ameliorating macrophage-mediated inflammatory damage symptoms."

Claims 2 to 5 and 7 to 11 related to specific embodiments of the uses according to claim 1 or 6.

III. The examining division only dealt with the issue of inventive step and considered that, in the light of document:

D2 Drake F.H. et al., Journal of Biological Chemistry, Vol. 271, No. 21, pages 12511- 12516 (1996)

the subject-matter of claim 1 of the sole request before it did not involve an inventive step in the sense of Article 56 EPC.

IV. The following further documents are cited in the present decision:

D6 Hill P.A. et al., J. Cell. Biochem., Vol. 56, pages 118-130 (1994);

D7 Troen B.R., Drug News Perspect., Vol. 17(1), pages 19-28 (2004);

D8 Gelb B.D. et al., Science, Vol. 273 (5279), pages 1236-1238 (1996);

D9 Park I. et al., J. Korean Medical Science, Vol. 11(2), pages 144-148 (1996);

D10 Delaissé J.M. et al., Biochem J., Vol. 192, pages 365-368 (1980);

D24 Votta B.J. et al., J. Bone and Miner. Res., Vol. 12, No. 9, pages 1396-1406 (1997).

V. Together with the statement setting out the grounds of appeal, the appellants filed on 2 October 2007 claims 1 and 2 of an auxiliary request, the claims of the appellants' main request being identical to those of the main request before the examining division.

VI. Claims 1 and 2 of the auxiliary request read as follows:

"1. Use of a compound which specifically inhibits cathepsin K activity of an osteoclast for the manufacture of a medicament for treatment of osteoporosis or arthritides."

"2. The use of claim 1, wherein the compound which specifically inhibits cathepsin K activity belongs to one of the following classes of compounds: fluoromethyl ketones, vinyl sulfones, peptide aldehydes, nitriles, α -ketocarbonyl compounds, including, for example, α -diketones, α -keto esters, α -ketoamides, and α -ketoacids, halomethyl ketones, diazomethyl ketones, (acyloxy)-methyl ketones, ketomethylsulfonium salts and epoxysuccinyl compounds."

VII. Accompanying a summons to oral proceedings, there was sent a communication expressing the board's provisional opinion.

VIII. Oral proceedings were held on 27 April 2010.

IX. The submissions by the appellants, insofar as they are relevant to the present decision, can be summarized as follows:

Main Request

- The skilled person reading document D2 would have had severe doubts as to the suitability of cathepsin K as a target for selective inhibitors in order to ameliorate bone resorption disorder symptoms. This is because the data in document D2 were

scientifically flawed and in contradiction to the established and prevalent understanding in the art that at least one or more of cathepsins L, B and S had to be inhibited in order to reduce bone resorption.

- In view of its deficiencies, document D2 was not the appropriate starting point for the assessment of inventive step.
- The suggestion in D2 to use cathepsin K inhibitors in treating excessive bone loss was not based on any scientific evidence. The document was scientifically and methodologically unsound and also contrary to the other prior art available at the priority date of the present application (documents D6, D9 and D10).
- The various molecular biology techniques were inadequate and not sufficiently controlled to support the conclusions drawn in document D2. The cDNA library on which the study described in document D2 was based had been isolated from a neoplastic osteoclastoma tissue. However, it was known that the expression of the cathepsin genes could be up-regulated in certain cancers.
- No biological function of cathepsin K was presented in document D2.
- Post-published document D7 acknowledged that Gelb et al. in document D8 (which was the academic publication related to the present application) were

the first to provide experimental data proving that cathepsin K was involved in bone resorption.

Auxiliary Request

- In claim 1 of this request, the conditions to be treated had been limited to osteoporosis or arthritides.
 - Claim 2 of this request specified the classes of inhibitors.
- X. The appellants request that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 11 filed with the letter dated 12 December 2005 (main request) or, as an auxiliary request, on the basis of claims 1 and 2 filed with the letter of 2 October 2007.

Reasons for the Decision

1. The only issue dealt with in the decision under appeal was that of inventive step (see section III supra), which becomes the only object of the present decision, too.

Closest prior art

Document D6

2. Document D6 is concerned with the use of cysteine proteinase inhibitors to reduce bone resorption. The authors of this document performed inhibition studies both on normal bone tissue isolated from mice and in

vivo, by injecting inhibitors directly into mice and subsequently observing the extent to which bone resorption was reduced (see pages 119-120). Four cystein proteinase inhibitors were tested (CA074, CA074Me, Ep475 and Ep453). Ep475, an inhibitor of cathepsins B, L, S and H that could not penetrate the cell membrane, was capable of inhibiting bone resorption (see page 126), implicating an extracellular activity in bone resorption. CA074Me, a cell permeable methyl ester derivative of the cathepsin B inhibitor CA074, was an equally effective inhibitor of bone resorption as Ep475 in an in vivo/in vitro assay, although cell-impermeable CA074 itself was an ineffective inhibitor of bone resorption (see page 125). These data suggested to the authors of document D6 that cathepsins B, L, and/or S were involved in bone resorption, with cathepsin B having an intracellular role.

Document D2

3. The authors of this document investigated mRNA expression of genes encoding cathepsins in human osteoclasts. They first sequenced portions of randomly chosen expressed sequence tag (EST) clones from an osteoclast cDNA library. Using this method, they found that 4% of the 5475 ESTs in the osteoclast library were from the cathepsin K gene (a novel cathepsin also named cathepsin O2 or cathepsin X), while the levels of cathepsin B and S were 100-200 times lower and no cathepsin L transcripts were observed. They also found very low levels of cathepsin K ESTs in libraries prepared from other tissues and tumours. In situ hybridization with a cathepsin K cDNA probe was also

performed, showing that cathepsin K mRNA expression was from osteoclasts in the osteoclastomas (as opposed to the other cells constituting the tumour). This documented specific expression in the osteoclasts. Similar in situ hybridization studies with probes for the other three cathepsin genes failed to detect any signal in osteoclasts. Two anti-sera (antibody C2 and antibody SR1) were raised against cathepsin K peptides which allowed the expression of the protein cathepsin K to be detected in the osteoclasts in osteoclastoma and osteophytes. In the light of these data the authors of document D2 concluded that selective inhibitors of cathepsin K could be useful in the treatment of diseases of excessive bone loss, such as osteoporosis (see page 12515, r-h column, last sentence).

4. The analysis above shows that document D6 suggested to inhibit cathepsins other than cathepsin K for fighting pathologic bone resorption, whereas document D2 suggested that selective inhibitors of cathepsin K could be useful for this purpose. Document D2 is thus closer to the claimed subject-matter than document D6.

The appellants maintain that document D6 rather than document D2 must represent the closest prior art because the latter document was scientifically and methodologically flawed (for more details, see points 11, 15 and 17 below). Hence, the skilled person, who was, by definition, very unwilling to take risks, would not have been inclined to follow the suggestion at the end of document D2. As an example of a study with a much more plausible background, document D6 could be cited (inhibition of cathepsins B, L, S, H, for fighting pathologic bone resorption). Similar

considerations were valid for document D10 (inhibition of cathepsins B and N for the same scope), document D7 (inhibition of cathepsin L and B for the same scope), document D9 (inhibition of cathepsin L to treat osteoporosis).

However, the board does not share the appellants' negative view toward the teaching in document D2 for the reasons given below (see points 14, 16 and 17) and therefore, document D2 represents the closest prior art.

5. Starting from document D2, the objective technical problem to be solved was the provision of a treatment for disorders involving excessive bone resorption.
6. The proposed solution was the use of compounds which specifically inhibited cathepsin K activity in osteoclasts.
7. The present patent application is based on the experimental demonstration that pycnodysostosis (an autosomal recessive osteochondrodysplasia characterized by osteosclerosis and short stature; see the present application on page 46, lines 2-4) is connected with a genetic lack of cathepsin K activity and that this deficiency affects only the patients' bone matrix resorption process, otherwise leaving the rest of the body intact. This experimental finding implies that inhibiting cathepsin K activity alone should be helpful in bone resorption disorders.

Moreover, pages 7-8 and 11-13 of the description provide technical information as to how to proceed for selecting specific cathepsin K inhibitors and measuring

inhibition (as confirmed by post-published document D24).

In view of the foregoing, the board is satisfied that the problem set out above (see point 5) has been solved.

8. The relevant question to be answered is whether or not the proposed solution could be derived in an obvious way from the prior art.
9. The board is prima facie of the opinion that document D2 provided a strong incentive to try specific cathepsin K inhibitors in the treatment for disorders involving excessive bone resorption (see document D2, page 12515, 1-h column, end of the first full paragraph: "Thus, the abundant, selective expression of cathepsin K, coupled with the apparent lack of other cysteine proteases, **strongly** suggests that this enzyme plays a key role in osteoclast-mediated bone resorption"; emphasis by the board).
10. The appellants argue that the teaching in document D2 would not have provided the skilled person with a reasonable expectation of success that specifically inactivating cathepsin K would have inhibited bone resorption.
11. The appellants' major objection was that the cDNA library on which the study in document D2 was based involved osteoclastoma (cancerous) cells or osteophytes instead of normal osteoclasts. The cDNA library was made from "fresh osteoclastoma tissue" (see page 12511, column 2, paragraph 4, under "Materials and Methods"). In situ hybridisation was carried out on "cryostat

sections from osteophytes and osteoclastoma tissue" (see page 12512, l-h column, paragraph 2). The Western blot shown in Figure 3 was from an "osteoclastoma lysate" (see page 12515, legend to Figure 3, and page 12512, l-h column, 3rd line from bottom). The immunocytochemistry was carried out on "samples of osteoclastoma tissue" (page 12512, r-h column, paragraph 2) or "undecalcified adult osteophytic bone". The appellants also emphasized that the cancerous cellular pathology of osteoclastoma cells was wholly different from that causing bone resorption disease (and it was hence not relevant for understanding how normal bone resorption occurred), the more so as the expression of the cathepsin genes could be up-regulated in certain cancers. Similarly, cathepsin K expression could have been up-regulated in the osteoclastoma cells on which the study in document D2 was based.

12. The board observes that osteoclasts were very rare cells (see document D2, page 12511, l-h column, line 11 and page 12515, l-h column, line 4 of the last paragraph). Therefore, osteoclastoma (cancerous) tissue was used as an enriched source of osteoclasts (ibidem, page 12515, r-h column, lines 7-8), which were separated from the other cells constituting the osteoclastoma. In fact, the authors of document D2 performed isolation and enrichment of the osteoclasts from an osteoclastoma tissue by disaggregation of the tumour, bead-coating of the osteoclasts and capture of the beads on a magnet, while the uncoated (non-osteoclast) cells were removed by extensive washing (see the passage beginning "Osteoclast cDNA Library" bridging pages 12511 and 12512). Since the cDNA library was made on the basis of isolated osteoclasts rather

- than the whole tumour tissue, the authors of document D2 termed it "osteoclast cDNA library" rather than "osteoclastoma cDNA library".
13. A similar approach was taken by the authors of post-published document D24 (see page 1399, under "Isolated human osteoclast resorption assay"). The board notes in passing that these authors, commenting on document D2, state that "a cDNA clone for human cathepsin K was obtained from an **osteoclast** library ⁽⁸⁾" (page 1399, 1-h column, lines 5-6; emphasis by the board; reference "(8)" being document D2).
14. In the board's view, the fact that the osteoclasts came from a cancerous tissue (osteoclastoma) did not mean that the osteoclasts themselves (rather than the chondrocytes, the osteoblasts, the osteocytes, the macrophages, the stromal cells, the mononuclear cells, etc) were neoplastic and/or that the osteoclasts expressed anomalous levels of cathepsins. There is no evidence before the board to this effect. Rather, the fact that the authors of document D24 used these osteoclasts isolated from osteoclastoma in a "human osteoclast resorption assay" confirms the board's opinion that osteoclasts from osteoclastoma tissue were as reliable as "natural" osteoclasts. The board thus disagrees with the appellant's proposition that osteoclastoma-derived osteoclasts were not relevant for understanding how normal bone resorption occurred.
15. The appellants further criticised the various molecular biology techniques of document D2, which they viewed as inadequate and not sufficiently controlled to support the conclusions drawn in the document. The generation

and random sequencing of cDNA/EST libraries (see the passage beginning "Cathepsin EST Frequency" on page 12512 of document D2) was not suited to the quantification of low abundance mRNA. In situ hybridization could detect only highly abundant mRNAs. Finally, the specificities of antibody C2 and antibody SR1 used for the immunochemical study had not been tested against other cathepsins.

16. However, the board observes that the patent application itself refers on page 52, lines 21-26 to the previous knowledge of the scientific community "that cathepsin K [was] the only cystein protease highly expressed in osteoclasts", citing four papers (Shi, Brömme, Tezuka and Inaoka) published in 1994 or 1995, i.e., before the publication date of document D2 (1996). In view of this, the skilled person would have considered the experimental data in document D2 as a further confirmation of the experimental findings of Shi, Brömme, Tezuka and Inaoka, referred to above, that cathepsin K was the only cystein protease highly expressed in osteoclasts.

In other words, the various molecular biology techniques used in document D2 would have been considered as fully reliable, because they were in keeping with the more recent scientific literature, while in divergence from less recent studies. The latter, however, involved e.g. antibodies and reagents designed for previously known cathepsins (see document D2, page 12515, end of l-h column) and the scope of the investigation in document D2 was to remedy the poor quality of these previous studies.

In conclusion, the appellants' arguments aimed at questioning the quality of the various molecular biology techniques used in document D2 are not convincing.

17. Finally, it was the appellants' view that no biological function of cathepsin K was presented in document D2.

In the board's judgement, the scope of the authors of document D2 was to identify **the** protease(s) (among all the possible cathepsins) involved in bone resorption (see document D2, page 12515, 1-h column, first full paragraph). It was already known that inhibition of these cystein proteases reduced bone resorption (see e.g. document D6). The mechanism by which this occurred was also known (inhibition of the enzymes responsible for the bone matrix degradation). Once the experimental results in document D2 pointed to cathepsin K as **the** protease, the skilled person would have concluded that inhibiting cathepsin K activity alone should be helpful in bone resorption disorders.

Therefore, the board does not share the appellants' view that no biological function of cathepsin K is presented in document D2.

18. The board also notes that shortly before the priority date of the present application, it became known, as acknowledged on page 52, lines 26-30 of the present application, that cathepsin K (owing to its high collagenolytic, elastinolytic and gelatinolytic activities) was the major protease involved in bone matrix resorption. This additional information would have provided the skilled person departing from

document D2 with an even higher expectation of success that specifically inactivating cathepsin K would have inhibited bone resorption.

19. For these reasons, claim 1 is found to lack an inventive step and thus the main request is not allowable under Article 56 EPC.

Auxiliary Request

20. In claim 1 of this request, the conditions to be treated have been limited to osteoporosis or arthritides.

Since document D2 explicitly mentions osteoporosis (see page 12515, r-h column, last sentence) as the pathology to be treated by means of the selective inhibitors of cathepsin K, no inventive step can be acknowledged for claim 1 of this request for the same reasons given above in relation to the main request. The latter is also not allowable under Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

P. Cremona

C. Rennie-Smith