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Datasheet for the decision of 11 October 2011

Case Number: T 1502/10 - 3.3.08

Application Number: 02768702.9

Publication Number: 1567641

IPC: C12N 9/52

Language of the proceedings: EN

Title of invention:
Proaerolysin containing protease activation sequences and methods of use for treatment of prostate cancer

Applicants:
University of Victoria Innovation & Development Corporation
Johns Hopkins University

Headword:
Proaerolysin/VICTORIA

Relevant legal provisions:
EPC Art. 56, 113(1)
EPC R. 103

Keyword:
"Main request: inventive step (yes)"
"Reimbursement of the appeal fees (no)"

Decisions cited:
T 0650/01

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1502/10 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 11 October 2011

Appellants: University of Victoria Innovation & Development Corporation
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and

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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 15 February 2010 refusing European patent application No. 02768702.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: M. Wieser
Members: T. J. H. Mennessier
D. S. Rogers

Summary of Facts and Submissions

I. The applicants (appellants) lodged an appeal against the decision of the examining division, whereby the European patent application No. 02 768 702.9 with publication number 1 567 641 was refused. The application, entitled "*Proaerolysin containing protease activation sequences and methods of use for treatment of prostate cancer*", originated from an international application published as WO 03/018611.

II. The decision was based on claims 1 to 39 of the request filed on 24 February 2009. The request was refused for reasons of lack of inventive step (Article 56 EPC) in view of document D1, which was considered to represent the closest state of the art, taken together with document D2 (see Section X, *infra*).

III. The appellants filed a statement setting out the grounds of appeal and requested reimbursement of the appeal fee as well as oral proceedings. Furthermore, accelerated processing of the appeal was requested because a product falling within the scope of the claims was entering phase III clinical trials.

IV. In a communication dated 24 January 2011, the board informed the appellants that their request for accelerated processing was granted.

V. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal attached to the summons to the oral proceedings, the board expressed its preliminary and non-binding views.

VI. In reply to the board's communication, the appellants filed further submissions with a letter dated 7 July 2011. The submissions were accompanied by a main request and two auxiliary requests to replace all the previous requests. Oral proceedings were still requested but only in case the board would not allow any one of the newly filed requests. The request for reimbursement of the appeal fee was maintained.

VII. The main request consisted of 36 claims of which claims 1, 17, 20, 23, 26 and 36 read as follows:

"1. A purified peptide comprising a variant proaerolysin amino acid sequence, wherein the variant proaerolysin amino acid sequence comprises a prostate-specific protease cleavage site and a functionally deleted furin cleavage site, wherein the prostate-specific protease cleavage site functionally replaces the furin cleavage site."

"17. The peptide of claim 1, wherein the peptide is immobilized to a surface."

"20. A peptide according to claim 1 for use in treating prostate cancer in a subject."

"23. A nucleic acid sequence that encodes the peptide of claim 1 for use in treating prostate cancer in a subject."

"26. A peptide according to claim 1 for use in a method of systematically treating prostate cancer in a subject, wherein the method comprises:
removing prostate cancer cells from the subject;
contacting the cells with the peptide of claim 1, thereby generating a cell lysate; and
administering the cell lysate to the subject."

"36. A purified nucleic acid sequence encoding the peptide of claim 1."

Claims 2 to 16 were dependent on claim 1. Claims 18 and 19 were dependent on claim 17. Claims 21, 22, 24, 25 and 30 to 32 were dependent on claim 20. Claims 27 to 29 and 33 to 35 were dependent on claim 26.

VIII. With a communication faxed on 20 September 2011, the board informed the appellants that the oral proceedings were cancelled.

IX. The following documents are referred to in the present decision:

(D1) US A 5 777 078 (published on 7 July 1998)

(D2) WO 98/20135 (published on 14 May 1998)

(D3) L. Abrami et al., The Journal of Biological Chemistry, Vol. 273, No. 49, 4 December 1998, pages 32656 to 32661

(D16) Declaration by S. R. Denmeade and T. Buckley dated 6 August 2008.

X. The submissions made by the appellants, insofar as they are relevant to the present decision, may be summarised as follows:

Reimbursement of the appeal fee

During the prosecution of the application and in the decision under appeal, the examining division consistently failed to allow the appellants to be heard according to the requirements of Article 113(1) EPC and it did not meet the requirement that a decision open to appeal has to be reasoned. In particular, the examining division failed to respond to the detailed arguments put forward by the appellants, failed to provide a proper technical basis for

its own position and failed to provide any reason for dismissing the substantial technical evidence provided by the expert declarations.

The examining division had made a number of assertions without appropriate documentary support. This was a serious procedural violation of Article 113 EPC and Rule 137(2) EPC (formerly Rule 86(2) EPC 1973).

By not detailing the technical grounds on which the experts' evidence was disregarded, the examining division committed another procedural violation.

The decision under appeal did not give reasons why the examining division considered the appellants' submissions and evidence not to be persuasive. This constituted a further substantial procedural violation.

Assessment of inventive step

The technical problem to be solved was the provision of a cytotoxin to be activated selectively in a prostate-specific manner to treat prostate cancer.

The prior art documents cited in the decision under appeal, either if taken alone or in any combination, did not contain a teaching that would enable the skilled person to arrive at the claimed subject-matter in an obvious way.

In the light of the existence of a large number of unknown variables, including the ability of a therapeutic agent to be formed in and secreted from the host cell, to oligomerise and therefore exhibit sufficient toxicity, to remain sufficiently localised within the prostate and sufficiently targeted to prostate tumour cells and to resist degradation by non-specific proteases, the skilled person would have had no reasonable expectation that an efficient therapeutic agent for prostate cancer as claimed could be prepared.

XI. The appellant requested that the decision under appeal be set aside, a patent be granted on the basis of the main request or one of the two auxiliary requests all filed under cover of the letter of 7 July 2011, and the appeal fee be reimbursed.

Reasons for the Decision

Reimbursement of the appeal fee

1. Reimbursement of the appeal fee is governed by Rule 103 EPC which states *inter alia* that such reimbursement should be equitable by reason of a substantial procedural violation.

2. The appellants' objection that the decision under appeal is not reasoned is not tenable. Indeed, the decision contains a detailed analysis of the three prior art documents D1, D2 and D3 and it explains at length why, in the opinion of the examining division, the subject-matter of claim 1 of the only request then on file did not involve an inventive step (see points 2 to 12 on pages 2 to 7 of the decision). Thus, the decision is reasoned as prescribed in Rule 111 EPC.

3. Furthermore, the board is satisfied that, as admitted by the appellants in their letter of 7 July 2011, the decision is only based on grounds and evidence on which the appellants, in a series of submissions filed in reply to official communications, have had an opportunity to present their comments, as prescribed by Article 113(1) EPC.

4. In their submissions sent to the examining division on 19 November 2009, which did not contain any new evidence, the appellants did not complain that their right to be heard had been violated during the written procedure (Article 113(1) EPC). If, nevertheless, they had this impression, it can be reasonably assumed that they would have used the opportunity to explain their position at the oral proceedings. Instead they withdraw their request for oral proceedings in said letter of 19 November 2009, that is one day before the scheduled date of the oral proceedings before the examining division.

5. The further objection that their declarative evidence was not taken into account is contradicted by their own comments in their submission of 19 November 2009.

6. The board considers that the examining division in its assessment of inventive step chose the wrong document as the closest prior art (see points 11 to 18, *infra*). However, this is to be regarded as an error of judgment by the examining division, not as a procedural violation.

7. In view of the above, the board is not convinced that the examining division committed a procedural violation, let alone a substantial one. Therefore, the request for reimbursement of the appeal fee is refused.

Main request

8. The claims are based on claims 1 to 34 and 43 to 44 of the application as published (the content of which corresponds to the content of the application as filed), taken together with the passage on page 16 thereof, lines 20 to 24, which describes the feature "*wherein the prostate-specific protease cleavage site functionally replaces the furin cleavage site*" of the peptide of claim 1. The claims are clear and supported by the description. Thus, the requirements of Articles 123(2) and 84 EPC are met.

9. The board, moreover, is satisfied that the application discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

10. There is no evidence before the board, that the claimed subject-matter is anticipated by the disclosure in any of the prior art documents on file. Thus, the requirements of Article 54 EPC are met.

Compliance with Article 56 EPC

11. The application was refused for the reason that the subject-matter of claim 1 of the request then on file, which differs from claim 1 of the main request only in that, after the word "*wherein*", the erroneous term "*protease-specific*" was used instead of the term "*prostate-specific*", did not involve an inventive step.

12. The board, when examining whether the examining division has correctly decided in this respect, follows the problem-solution approach, which requires, as a first step, to select the document which represents the closest prior art.

13. It is established case law that the closest state of the art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common (see in particular, decision T 650/01, point 4.3 of the Reasons).

14. The present application is concerned with the treatment of prostate cancer (see pages 1 and 2 of the published application). The decision under appeal refers to three prior art documents, designated as documents D1, D2 and D3.

15. Document D1 describes a delivery agent which is a cell-specific ligand capable of specifically binding to a molecule or structure on the surface of a target cell. This ligand, which is preferably an antibody, is linked to a pore-forming agent. Preferably, the pore-forming agent is a bacterial polypeptidic exotoxin, such as •HL (alpha-hemolysin), a toxin secreted by *Staphylococcus aureus*, or **aerolysin** (see column 2, lines 13 to 17 and column 7, lines 32 to 36).

15.1 The pore-forming agent, which has been modified to make it inactive, can be converted to its active lytic form under specific activating conditions or by a specific substance, preferably by an enzyme. For the activation a peptide of at least ten amino acids is added into a glycine-rich loop of an internal domain of the pore-forming agent. The enzymatic cleavage of the amino acid extension restores the lytic activity (see column 3, lines 30 to 49).

15.2 The only activatable pore-forming agents described in the experimental part of document D1 are mutants of •HL (see Example 1, columns 13 to 16), which are activated by Lys/Arg-directed proteases (see Example 1, columns 13 to 16), or are responsive to metal ions (see Example 2, column 16) or are photoactivable (see Example 3, columns 16 to 22). *In vitro* tests of a conjugate made of a •HL mutant linked to an antibody and activated by trypsin are described in Example 5 (see columns 23 to 25).

15.3 Document D1 in columns 2 and 7 (see point 13, *infra)* does not refer to proaerolysin, as present claim 1, but to aerolysin, its active form obtainable upon cleavage by furin. It does not mention prostate cancer let alone any targeted treatment thereof.

16. Document D2, as the application at issue, describes protoxins which become active upon a proteolytic cleavage by a prostate-specific-protease which are useful in the targeted treatment of prostate cancer.

16.1 The document is concerned with *Pseudomonas* exotoxin-A proproteins, which are not pore-forming and which have been engineered to replace their furin recognition site, contained in a cysteine-cysteine loop, by a site recognised by a protease made or secreted by a cell targeted for death, for example, a cancer cell (see page 3, lines 2 to 23).

16.2 More precisely, document D2 describes chimeric immunotoxins targeted to the human transferrin receptor, whose furin-specific processing site has been altered to render it cleavable by the cancer-expressed protease PSA (see Sections I to VII on pages 48 to 54). Two mutated chimeric immunotoxins with different PSA cleavage sites were produced. Their cytotoxicity was tested on six human cancer cell lines including two prostate cancer cell lines (see Section VIII on pages 54 to 55).

17. Document D3 shows that conversion of proaerolysin into the active toxin aerolysin in CHO cells occurs primarily via the action of furin which recognises a sequence contained in a mobile loop near the C-terminus of the protoxin (see the abstract on page 32656 and the first full paragraph on the hand-left column of page 32660). The document does not contain any information concerning a possible alteration or replacement of the furin cleavage or a treatment of prostate cancer.

18. In view of the above review of the three documents, D2 is the document which discloses subject-matter conceived for the same purpose and aiming at the same objective as the claimed invention, namely the treatment of prostate cancer, and which has the most relevant technical features in common. Therefore, the board concludes that document D2 - not

document D1 as decided by the examining division - represents the closest state of the art for the assessment of inventive step.

19. Starting from document D2, the technical problem to be solved is the provision of a further protoxin, which is capable of being activated by a prostate-specific protease and is useful in the treatment of prostate cancer. The solution according to claim 1 is a peptide comprising a proaerolysin variant wherein the furin cleavage site has been replaced by a prostate-specific protease cleavage site. Example 2 of the application discloses such peptide, specifically activated by PSA (prostate-specific antigen), which shows a 500-fold difference in toxicity against PSA-producing versus non-PSA producing human cancer cell lines. Thus, the board is convinced that the technical problem has indeed been solved by the subject-matter of claim 1.

20. The final question to be answered is whether the skilled person would have found any incentive, either in document D2 itself, or upon combination with the disclosure in the other prior art documents on file, to change the disclosure in the document representing the closest state of the art and to arrive at the subject-matter of claim 1 in an obvious way.

21. The subject-matter of claim 1 is distinguished from the disclosure in document D2 in so far as, instead of *Pseudomonas* exotoxin-A proproteins, which are not pore-forming, proaerolysin is engineered to replace its furin recognition site by a prostate-specific protease cleavage site.

22. No information pointing in this direction can be found in document D2 itself. It does not mention proaerolysin at all and, in its experimental part, it is exclusively concerned with *Pseudomonas* exotoxins which are fundamentally different from the channel forming toxins used in the present application (see the explanations in document D16). The mechanism used in document D2 for the activation of the inactivated *Pseudomonas* exotoxins is categorically different from the one used in the present application for the activation of proaerolysin (see points 16.1 and 16.2, *supra*).

23. Document D1 describes pore-forming agents (other than proaerolysin) that do not contain any prostate-specific protease cleavage site. Document D1 gives no suggestion to replace the *Pseudomonas* exotoxin-A proproteins of document D2 by proaerolysin.

24. Document D3 describes the furin mediated conversion of proaerolysin into its active form aerolysin. However, it does not refer to any modified form of proaerolysin wherein the furin cleavage site has been deleted or replaced by another site and to possible therapeutic uses of such a

modified molecule. Therefore, also document D3 provides no incentive to the skilled person.

25. Therefore, the board decides that the skilled person would not have been in a position to arrive at the proaerolysin variants of claim 1 in an obvious way, neither when considering the disclosure in document D2 alone nor in combination with the other prior art documents on file. Thus, the board concludes that the subject-matter of claim 1 involves an inventive step.

26. A similar conclusion is reached with respect to claims 17, 20, 23, 26 and 36, the subject-matter of which is defined by a reference back to the peptide of claim 1 and claims dependent thereon (see Section VIII, *supra*). Thus, the subject-matter of claims 1 to 36 involves an inventive step and the main request as a whole complies with the requirements of Article 56 EPC.

27. In view of the positive conclusion reached with respect to the main request there is no need to consider the auxiliary requests.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent on the basis of claims 1 to 36 of the main request filed under cover of the letter of 7 July 2011, a description to be adapted thereto, with Figures 1 to 4 and 5A to 5M of the application as published and sequence listing pages 1 to 30 of the application as published.

3. The request for reimbursement of the appeal fee is refused.

The Registrar The Chairman

A. Wolinski M. Wieser