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Datasheet for the decision of 05 November 2008

Case Number: T 0873/06 - 3.3.04

Application Number: 98923673.2

Publication Number: 0983076

IPC: A61K 35/74

Language of the proceedings: EN

Title of invention:
Oxalate-degrading microorganisms or oxalate-degrading enzymes for preventing oxalate related disease

Applicant:
OxThera, Inc.

Headword:
Oxalate related disease/OXTHERA

Relevant legal provisions:
EPC Art. 54, 56, 84, 123(2)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request, novelty (yes)"
"Inventive step (yes)"
"Clarity (yes)"
"Added matter (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0873/06 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 05 November 2008

Appellant: OxThera, Inc.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 16 December 2005 refusing European patent application No. 98923673.2 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chair: U. Kinkeldey
Members: B. Claes
R. Moufang

Summary of Facts and Submissions

I. European patent application 98923673.2 was filed as international patent application PCT/US98/10495 and was published as WO98/52586 (which will be referred to in the present decision as the "application" or the "application as filed". The title of the application is *"Oxalate-degrading microorganisms or oxalate-degrading enzymes for preventing oxalate related disease"*.

Claim 13 and 20 of the application as filed read:

"13. A composition for reducing absorption from the intestines of dietary oxalate wherein said composition comprises a material selected from the group consisting of oxalate-degrading microbes and oxalate-degrading enzymes."

"20. The composition, according to claim 13, wherein said composition is formulated to reduce deactivation in the stomach."

II. The examining division refused the application based on the grounds that the subject-matter of the claims before them lacked novelty and/or inventive step.

III. The appellant (applicant) lodged an appeal against the decision and filed with the statement setting out the grounds for appeal a new main request and three auxiliary requests, as well as two documents with experimental data.

IV. In a communication dated 5 September 2008, the board expressed its preliminary opinion that claim 1 of each of the requests lacked inventive step.

V. In reply to that communication the appellant filed observations in a letter dated 3 October 2008, which was accompanied anew by a main request and four auxiliary requests.

VI. Oral proceedings took place on 5 November 2008. At these oral proceedings, the appellant filed a new main request comprising claims 1 to 6 to replace all former requests on file. Claim 1, the only independent claim of this new main request, was largely based on the formulation of claim 1 of the main request filed with appellant's letter of 3 October 2008 and read:

"1. A composition for the treatment of oxalate related disease in humans by reduction of oxalate in the intestines and thereby reducing the concentration of oxalate in kidney fluid, wherein said composition comprises a material selected from the group consisting of oxalate-degrading microbes and oxalate-degrading enzymes, wherein the composition is formulated to reduce deactivation in the stomach and wherein said composition is coated with a material which degrades in the small intestine."

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

D1: US 5,286,495

D7: Daniel *et al.* (1993), Microbial Ecology in Health and Disease, Vol. 6, pages 277 to 283.

Appendix 1: Comparative study of D1-type alginate microcapsules and enteric coated gel capsules; filed by the appellant with letter of 25 April 2006.

Annex 4: Cellulose Acetate Phthalate (CAP) Microencapsulating; filed by the appellant with letter of 3 October 2008.

VIII. The appellant has argued in essence as follows:

Article 123(2) EPC

– The claims according to the main request are based on claims 13 to 21, on page 1, lines 27 to 29, on page 4, lines 14 to 16 and 29 to 30 and on page 7, lines 8 to 11 of the application as filed.

Inventive step

– None of the cited documents renders the subject-matter claimed obvious to the skilled person, neither do, in particular, documents (D1) and (D7).

– The gist of document (D1) was the encapsulation of *inter alia* oxalate-reducing microbes with a view to introducing them into the human or animal body where they can continue to produce and release enzyme but are not subject to attack from the immune system (column 5, lines 5 to 11).

– Document (D7) disclosed that although administered *O. formigenes* could colonise and degrade oxalate in the rat intestinal tract, this colonisation did not however markedly influence urinary oxalate excretion which thus gave little support to the hypothesis that urinary oxalate excretion in rats might be altered by colonisation by *O. formigenes*.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 6 of the new Main Request filed at the oral proceedings.

Reasons for the Decision

Added matter - Article 123(2) EPC

1. The board is satisfied that the features of claim 1 can be derived from the application as filed. The wording of the claim is in particular based on a combination of claims 13 and 20 as filed combined with the following indicated passages disclosing the following further features:

On page 4, lines 14 to 15, the application states that "[t]*he subject invention pertains to the introduction of oxalate-degrading bacteria and/or enzymes into the human intestinal tract where the activity of these materials reduces the absorption of oxalate and reduces the risk of disease due to oxalate.*" and on lines 29 to 30 that "[e]*nrichment of the contents of the small intestine with one or more species of oxalate-degrading bacteria causes a reduction of oxalate in the*

intestinal contents.". Thus, the feature that the composition is to reduce oxalate in the intestines is disclosed in the application as filed.

On page 5, lines 5 to 9 the application discloses that "[t]*he gel cap material is preferably a polymeric material which forms a delivery pill or capsule that is resistant to degradation by the gastric acidity and pepsin of the stomach but is degraded with concomitant release of oxalate-degrading materials by the higher pH and bile acid contents in the proximal small intestine*." and on page 7, lines 8 to 11, that "[c]*ells from a selected single strain or mixtures of known strains can be treated as needed (e.g., freeze dried with trehalose or glycerol) to preserve viability and are then placed in capsules designed to protect the cells through their passage through the acid stomach (enteric coated capsules)*.". Thus, the feature that the composition is coated with a material which degrades in the small intestine has a basis in the application as filed.

On page 1, lines 27 to 29, the application states that "[t]*he concentration of oxalate in kidney fluids is critical, with increased oxalate concentrations causing increased risk for the formation of calcium oxalate crystals and thus the subsequent formation of kidney stones*." and on page 4, lines 19 to 21 that "... *where their metabolic activities reduce the amount of oxalate available for absorption from the intestine and thus reduce concentrations of oxalate in kidney and other cellular fluids*.". Thus, the feature that the composition reduces the concentration of oxalate in kidney fluids is disclosed in the application as filed.

On page 1, lines 11 to 16, the application discloses that besides kidney-urinary tract stone disease (urolithiasis), also other disease states have been associated with excess oxalate such as vulvodynia, oxalosis associated with end-stage renal disease and with Crohn's disease and other enteric disease states and on page 4, lines 14 to 16 that "[t]he subject *invention pertains to the introduction of oxalate-degrading bacteria and/or enzymes into the human intestinal tract where the activity of these materials reduces the absorption of oxalate and reduces the risk of disease due to oxalate*.". Thus, the feature that the composition is for the treatment of oxalate related disease in humans is disclosed in the application as filed.

2. Dependent claims 2 to 6 find direct support in the wording of claims 14 to 16, 18 and 19 contained in the application as filed and which are dependent on claim 13 as filed.

3. In view of the above considerations, the claims comply with the requirements of Article 123(2) EPC.

Clarity - Article 84 EPC

4. The board is of the view that, with the above-mentioned amendments introduced into the claims, the matter for which protection is sought is defined in a clear and unambiguous manner.

Novelty - Article 54 EPC

5. Document (D1) discloses the encapsulation of *Oxalobacter formigenes* both for enteric and for intraperitoneal administration and discloses two types of encapsulation. A first approach is based on alginate encapsulation. As the appellant could show however in appendix 1, i.e. a comparative study of D1-type alginate microcapsules and enteric coated gel capsules filed by the appellant with letter of 25 April 2006, alginate capsules do not disintegrate in the small intestine. A second approach concerns cellulose acetate phthalate (CAP) microspheres. However, in annex 4, i.e. an experimental report filed by the appellant with letter of 3 October 2008, the appellant has experimentally shown that CAP microspheres prepared in accordance with the preparation process as described in example 5 of document (D1) display a 99,5% loss in activity and a 100% loss in viability of the microbial cells. Accordingly, the disclosure in document (D1) does not disclose a composition in accordance with claim 1.

6. The board is furthermore satisfied that also none of the other prior art documents cited during the examination procedure disclose a composition comprising a material selected from the group consisting of oxalate-degrading microbes and oxalate-degrading enzymes wherein the composition is coated with a material which degrades in the small intestine.

7. In view of the above considerations, the board considers the subject-matter of claim 1 and the claims dependent thereon novel.

Inventive step - Article 56 EPC

8. To assess whether or not a claimed invention meets the requirements of Article 56 EPC the boards of appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention.

9. Although document (D1) discloses the encapsulation of *Oxalobacter formigenes* both for enteric and for intraperitoneal administration, whereby the former is based on CAP and the latter is based on alginate encapsulation (see point 5, *supra*), the document is silent, both generally and experimentally, on the fact whether or not such compositions are capable of reducing the oxalate content in the intestines.

Document (D7) on the other hand relates to the intestinal colonisation of laboratory rats by *O. formigenes* and the effects thereof on the urinary and faecal excretion of dietary oxalate (see e.g. the title) with a view to study bacterial degradation of oxalate in the mammalian intestinal tract and its influence on the absorption and excretion of dietary oxalate (page 277, sentence bridging both columns and page 281, lines 25 to 30) and thus a possible

therapeutic application of the bacteria in the intestine for the management of the urinary oxalate and related diseases. The board therefore considers that document (D7) represents the closest prior art.

10. Document (D7) discloses experiments concerning the colonisation of the rat intestinal tract by *O. formigenes*. Suspensions of viable *O. formigenes* are administered intragastrically (see page 278, right hand column, lines 3 to 7) and subsequently the fate of dietary oxalate was measured in urinary and faecal excretion samples as well as the appearance of carbon-14 from [^{14}C]oxalate in expired CO_2. In short, the results (page 279, right hand column, line 3 to page 280, right hand column, line 3 and tables 1 to 3) of the experiments showed no significant change in urinary and faecal oxalate excretion expressed as a percentage of the daily intake of oxalate, whereas intragastrically inoculated rats excreted approximately 10-fold more carbon-14 as expired CO_2 than uninoculated rats. It was therefore concluded in document (D7) that although *O. formigenes* colonised and degraded oxalate in the rat intestinal tract, under the applied dietary conditions, this colonisation did not markedly influence urinary oxalate excretion (abstract, last sentence) and that these results gave little support to the hypothesis that urinary oxalate excretion in rats might be altered by colonisation by *O. formigenes* (page 282, line 1 to 3).

11. The problem to be solved by the subject-matter of claim 1 in the light of the disclosure in document (D1) is therefore to provide a composition for the treatment

of oxalate related diseases by reducing the concentration of oxalate in kidney fluids.

12. The subject-matter of claim 1 solves this problem by the provision of a composition comprising oxalate-degrading microbes or enzymes which can reduce oxalate in the intestines and which is formulated to reduce deactivation in the stomach and is coated with a material which degrades in the small intestine. In view of the experiments and results in examples 3 and 4 of the application, the board is convinced that the claimed subject-matter solves this problem.

13. The authors of document (D7) consider as a possible reason for their results (see point 10, *supra*) the fact of the high calcium content of the diet (see page 281, left hand column, last paragraph). The document concludes consequently that "[w]*e believe, however, that different results would be obtained with less calcium in the diet and that it would be premature to conclude that the present information can be extrapolated to other diets or to humans or other animals that are colonised in hindgut sites by anaerobic oxalate-degrading bacteria.*". Document (D7) therefore does not render obvious or suggest to the skilled person to formulate an encapsulated composition containing *O. formigenes* or enzymes thereof for the reduction of oxalate in the intestine thereby reducing the concentration of oxalate in the kidney fluids, but rather suggests further research on the physiological level (dietary calcium). Document (D7) does not therefore render the subject-matter of claim 1 obvious to a skilled person.

14. The board notes that also none of the further prior art documents cited during the examination proceedings, including document (D1), provides further incentives to the skilled person, which go beyond the theoretical level, as to the suitability of oral administration, (including the passage through the stomach) of oxalate degrading microbes or enzymes for reducing the concentration of oxalate in the kidney and thus in the treatment of oxalate related diseases in humans.

15. In view of the above considerations, the subject-matter of claim 1, and of any claim dependent thereon, involves an inventive step.

16. As the board is satisfied that the other requirements of the EPC are also met, the main request as filed during the oral proceedings before the board forms a basis for the grant of a patent.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent on the basis of claims 1 to 6 of the new main request filed at the oral proceedings and a description yet to be adapted.

The Registrar | The Chair

P. Cremona | U. Kinkeldey