Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 5 July 2017

Case Number: T 1252/13 - 3.3.04

Application Number: 05789469.3

Publication Number: 1809751

IPC: C12N15/82, A01H5/00

Language of the proceedings: EN

Title of invention:
Collagen producing plants and methods of generating and using same

Patent Proprietor:
CollPlant Ltd.

Opponent:
Fibrogen, Inc.

Headword:
Collagen producing plants/COLLPLANT

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
Amendments - allowable (no)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

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 1252/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 5 July 2017

Appellant I: (Patent Proprietor)	CollPlant Ltd. 3 Sapir Street 74140 Nes Ziona (IL)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Appellant II: (Opponent)	Fibrogen, Inc. 409 Illinois Street San Francisco, CA 94158 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 22 March 2013 concerning maintenance of the European Patent No. 1809751 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	R. Morawetz
	P. de Heij

Summary of Facts and Submissions

I. The appeals of the patent proprietor (hereinafter "appellant I") and the opponent (hereinafter "appellant II") lie against the decision of the opposition division maintaining European patent No. 1 809 751 in amended form.

II. The patent at issue has the title "*Collagen producing plants and methods of generating and using same*" and was granted in respect of European patent application No. 05 789 469.3 which was published as WO 2006/035442 (hereinafter "application as filed").

III. An opposition was filed invoking the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) under Article 100(a) EPC and the grounds under Article 100(b) and (c) EPC.

IV. The opposition division decided that the main request failed the requirements of Article 123(2) EPC and that auxiliary request I before it failed the requirements of Article 123(3) EPC. It maintained the patent on the basis of auxiliary request II.

V. Appellant I filed with its statement of grounds of appeal a main request and auxiliary requests I to IV, wherein auxiliary request IV corresponded to auxiliary request II underlying the decision under appeal.

VI. In response to appellant II's grounds of appeal, appellant I replaced the pending claim requests with a main request and auxiliary requests 1 to 39, wherein auxiliary request 32 corresponded to auxiliary request II underlying the decision under appeal.

VII. Oral proceedings before the board took place on 4 and 5 July 2017. In the course of the oral proceedings appellant I withdrew all pending claim requests except for auxiliary request 32.

Claim 1 of auxiliary request 32 reads:

"1. A genetically modified plant or isolated plant cell comprising an exogenous polynucleotide sequence encoding at least one type of a collagen alpha chain and an exogenous polynucleotide sequence encoding human P4H, each of said at least one type of collagen alpha chain and said human P4H being attached to a vacuole transit peptide, wherein said at least one type of collagen alpha chain and said human P4H are devoid of an ER retention sequence and wherein said at least one type of collagen alpha chain is accumulated in a vacuole devoid of endogenous P4H activity."

At the end of the oral proceedings the chairwoman announced the board's decision.

VIII. The arguments of appellant I submitted in writing and during the oral proceedings and relevant for the present decision may be summarised as follows:

Auxiliary request 32 (sole claim request)

Article 123(2) EPC - claim 1

"attached to a vacuole transit peptide"

The attachment of collagen chains to a signal sequence to achieve targeting to a subcellular compartment devoid of endogenous prolyl-4-hydroxylase (P4H) was explicitly mentioned at page 13, last paragraph to

page 14, first paragraph of the application as filed, and the same passage referred to the example section for additional examples of suitable signal sequences (see page 14, lines 4 to 6). In example 2, at page 28, last sentence, the attachment to a "*vacuole transit peptide*" was explicitly mentioned.

Accordingly, based on the general part of the description (page 14, lines 5 to 7), the vacuole transit peptide was disclosed *per se,* independently of any specific experimental approach and feature combination.

Subcellular compartments were described at page 12, in the second full paragraph, as including the vacuole and the examples centred on the vacuole. Therefore, the selection of the vacuole as a subcellular compartment for accumulation was disclosed in the application.

On the basis of original claims 22 and 25, which taught using "*signal*" peptides for targeting to a vacuole, the skilled person would have understood that said teaching was tantamount to the use of vacuole transit peptides. The term "*vacuole transit peptide*" was synonymous with the term "*vacuole signaling peptide*".

The third paragraph at page 3 and the third full paragraph at page 15 served as a basis for the attachment of a vacuole transit peptide also to P4H. From these passages it followed that the same modifications were to be made to both the collagen and the P4H protein. Thus, if collagen was directed to the vacuole, then so was P4H.

"devoid of an endoplasmic reticulum (ER) retention sequence"

The feature "*devoid of an ER retention sequence*" in the context of collagen and P4H was supported by original claims 4 and 6; page 4, third full paragraph; page 5, sixth paragraph; page 6, penultimate paragraph, and page 7, second paragraph. These passages clearly and unambiguously established that the features "*devoid of an ER targeting sequence*" and "*devoid of an ER retention sequence*" were alternatives.

Combination of the features "attached to a vacuole transit peptide" and "devoid of an ER retention sequence"

Each of the features "*attached to a vacuole transit peptide*" and "*devoid of an ER retention sequence*" was individually disclosed in the application as filed.

The skilled person was moreover aware of the fact that proteins which were targeted to the vacuole were passing through the ER. Therefore, the skilled person would have understood that a protein targeted to the vacuole had to have a vacuole targeting sequence and should be devoid of an ER retention sequence. The combination of the features "*attached to a vacuole transit peptide*" and "*devoid of an ER retention sequence*" was understood by the skilled person to be a technical prerequisite to achieve targeting to the vacuole. Therefore, the combination of the two latter features was also directly and unambiguously disclosed for the skilled person.

Figure 2 depicted various co-transformation approaches involving the absence of an ER retention sequence and

the presence of a vacuole transit peptide, see column "*vacuole*", item 3 of Figure 2 in combination with example 2, Table 1 at page 27, and page 28, last paragraph of the section entitled "*Construction of plasmids*". Claim 1 was thus directed to what was shown in the examples.

At page 14, in the third full paragraph, the application as filed referred to embodiments featuring the combination of the two features.

Page 15, third full paragraph, provided a basis for the combination of the features "*attached to a vacuole transit peptide*", "*devoid of an ER retention sequence*" and "*P4H*".

Nothing in the application as filed would prompt another reading, *i.e.* that the features "*attached to a vacuole transit peptide*" and "*devoid of an ER retention sequence*" could not be combined.

IX. The arguments of appellant II submitted in writing and during the oral proceedings and relevant for the present decision may be summarised as follows:

Auxiliary request 32 (sole claim request)

Article 123(2) EPC - claim 1

"attached to a vacuole transit peptide"

The paragraph in the application as filed bridging pages 13 and 14 related to collagen, not to P4H, and did not mention the vacuole. Therefore, this passage did not provide any basis for a vacuole transit peptide attached to each of collagen and P4H.

The feature "*attached to a vacuole transit peptide*" was disclosed on page 28, line 23 within a list of three alternatives encompassing also the attachment to "*apoplasm transit peptide*" and "*devoid of any transit peptide*". There was no pointer in this passage to vacuole targeting in particular. The claim limited the list of three alternatives to the attachment of a "*vacuole transit peptide*" for both collagen and P4H. This involved a selection of the signal and of the peptide.

Also claim 3 as filed and the fifth paragraph on page 5 disclosed two alternative signal peptides, and only in the context of collagen. The restriction to "*vacuole transit peptide*" was also a selection from this disclosure.

Co-sequestration of collagen chains and P4H as a goal was disclosed in the application as filed on page 3, third paragraph and page 15, fourth paragraph, but it was not disclosed that collagen and P4H had to have the same kind of modifications.

"devoid of an ER retention sequence"

Two alternatives were disclosed in the application as filed as regards the ER sequences, *i.e.* "*devoid of an ER targeting sequence*" and "*devoid of an ER retention sequence*". The description was consistent in describing these as two distinct, equal alternatives. Thus, claim 1 included a double selection of the feature "*devoid of an ER retention sequence*", *i.e.* for collagen and for P4H.

Claim 4 as filed disclosed the collagen alpha chain but

not P4H and it also referred to both alternatives, *i.e.* "*devoid of an ER targeting or retention sequence*". Also here, the restriction to "*devoid of an ER retention sequence*" was a selection.

Claim 7 as filed disclosed P4H but, like claim 4, it also referred to both alternatives, *i.e.* "*devoid of an ER targeting or retention sequence*". Again, restriction to "*devoid of an ER retention sequence*" was a selection.

There was no pointer to the selection of "*devoid of an ER retention sequence*" in the application as filed, which did not disclose it as preferred over "*devoid of an ER targeting sequence*".

On the contrary, the application as filed pointed to the other alternative, i.e. to "*devoid of an ER targeting sequence*". Thus, page 14, lines 10 to 14 disclosed that collagen alpha chains natively included an ER targeting sequence which directed expressed collagen into the ER where it was post-translationally modified (including incorrect hydroxylation) and that removal of this sequence led to cytoplasmic accumulation of collagen chains.

Collagen did not contain an ER retention sequence and so the description only described the deletion of the ER targeting sequence from collagen that was naturally devoid of an ER retention sequence.

Table 1 on page 27 of the application described the polynucleotide sequences designed for expression in tobacco plants. The fifth column of this table confirmed that every single human collagen had its "*ER signal*" deleted. This was the ER targeting signal.

Both P4H subunits exemplified in Table 1 had the ER targeting signal deleted, while the P4H beta subunit also had the ER retention signal (KDEL) deleted. There was no disclosure of a P4H that was devoid of an ER retention sequence, only.

According to the case law, examples could be relied on for indicating preferred features. However, the disclosure of page 14 of the application was consistent with the disclosure in the example, see in particular Table 1 on page 27. The ER targeting signal had been removed in both collagen alpha chains and in both P4H subunits, while the ER retention signal had only been removed from the P4H alpha subunit. Thus, removal of the ER targeting sequence, or of both the targeting and retention sequences, was disclosed in the application as filed, but not removal of only the ER retention sequence.

Combination of the features "attached to a vacuole transit peptide" and "devoid of an ER retention sequence"

The selection of the term "*devoid of an ER retention sequence*" and its combination with the numerous other selected features included in claim 1 presented the skilled person with new information that was not disclosed in the application as filed.

None of the examples disclosed all the features of claim 1 in combination, because in the examples the endogenous ER targeting sequence was removed.

X. Appellant I requested that appellant II's appeal be dismissed.

Appellant II requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

Auxiliary request 32 (sole claim request)

Article 123(2) EPC - claim 1

1. The subject-matter of claim 1 is directed to a genetically modified plant or isolated plant cell comprising an exogenous polynucleotide sequence encoding at least one type of a collagen alpha chain and an exogenous polynucleotide sequence encoding human prolyl-4-hydroxylase (P4H), wherein the collagen and human P4H are each attached to a vacuole transit peptide and are devoid of an endoplasmic reticulum (ER) retention sequence.

2. It is undisputed between the parties that the claimed combination of features - that the collagen and human P4H are each attached to a vacuole transit peptide and are devoid of an ER retention sequence - is not explicitly disclosed in the application as filed.

3. At issue is thus whether or not the claimed combination of features can be derived directly and unambiguously, using common general knowledge, from what is explicitly disclosed in the application as filed, *i.e.* whether the combination is implicitly disclosed.

4. Appellant I indicated a basis in the application as filed for the modifications of the collagen alpha

chain, *i.e.* attached to a vacuole transit peptide and devoid of an ER retention sequence, and submitted that the application as filed disclosed that the same modifications were to be made to both the collagen and the P4H protein (see section VIII above). Therefore, in the following analysis the board will focus first on the modifications in the context of the collagen alpha chain.

"attached to a vacuole transit peptide"

5. The present invention aims at expressing at least one type of a collagen alpha chain and exogenous P4H in a plant so as to enable accumulation of the collagen alpha chain and exogenous P4H in a subcellular plant compartment devoid of endogenous P4H activity (see page 3, fourth paragraph of the application as filed).

6. As to how this accumulation is achieved, the application as filed discloses that "*accumulation of the expressed collagen in a subcellular compartment devoid of endogenous P4H activity can be effected via any one of several approaches. For example the expressed collagen chain can include a signal sequence for targeting the expressed protein to a subcellular compartment such as the apoplast or an organelle (e.g. chloroplast). Examples of suitable signal sequences include the chloroplast transit peptide (included in Swiss-Prot entry P07689, amino acids 1-57) and the Mitochondrion transit peptide (included in Swiss-Prot entry P46643, amino acids 1-28*" (see paragraph bridging pages 13 and 14). Additional examples of suitable signal sequences for expression of collagen chains in plants are said to be provided in the examples section (*ibid.*).

7. The examples section discloses under the heading "*Signal peptides*" the vacuole signal sequence of the barley gene for Thiol protease aleurain precursor and the apoplast signal of Arabidopsis thaliana endo-1,4-beta-glucanase. Under the heading "*Construction of plasmids*" it further discloses that "*each of the above described coding sequences was translationally fused to a vacuole transit peptide or to an apoplasm transit peptide or was devoid of any transit peptide sequences, in which case cytoplasmic accumulation is expected*" (see page 28, lines 23 to 25).

8. Thus, the application as filed discloses targeting of the collagen alpha chain to various subcellular compartments including the apoplast, the vacuole, the cytoplasm, the chloroplast and mitochondria, involving - with the exception of targeting to the cytoplasma - the use of a specific transit peptide (see points 6 and 7 above). In the board's judgement, the choice of attaching a vacuole transit peptide to the collagen alpha chain thus represents a selection from the various possibilities disclosed in the application for targeting to subcellular compartments.

9. In the board's view, there is no pointer to this particular selection in the application as filed. Apoplast, vacuole, cytoplasm, chloroplast and mitochondria are disclosed in the description as equal, alternative subcellular compartments which are all devoid of endogenous P4H activity (see page 12, third paragraph). Nor is any preference for any subcellular compartment discernible from the examples, as the collagen alpha chain is targeted to either the apoplasm, the vacuole or the cytoplasm (see examples 1 to 3, and Figure 2).

"devoid of an ER retention sequence"

10. As regards the combination of the collagen alpha chain with the absence of ER sequences, the application as filed discloses consistently two alternatives as follows: "*the at least one type of a collagen alpha chain is devoid of an ER targeting or retention sequence*" (see page 5, sixth paragraph, page 6, penultimate paragraph, and claim 4).

11. Accordingly, the choice to combine the collagen alpha chain with the feature "*devoid of an ER retention sequence*" represents a further selection. In the board's view, there is likewise no pointer to this particular selection in the application as filed, for the following reasons.

12. The application as filed discloses that "*collagen alpha chains natively include an ER targeting sequence which directs expressed collagen into the ER where it is post-translationally modified (including incorrect hydroxylation). Thus, removal of the ER targeting sequence will lead to cytoplasmic accumulation of collagen chains which are devoid of post translational modification including any hydroxylations. Example 1 of the Examples section which follows describes generation of collagen sequences which are devoid of ER sequences*" (see page 14, third paragraph).

13. The examples section discloses that the ER targeting sequence was removed from the polynucleotide sequences encoding the collagen alpha chain, thus disclosing the collagen chain as being devoid of its endogenous ER targeting sequence whilst being silent about the collagen being devoid of an ER retention signal (see

Examples 1 and 2 and Table 1).

14. Even if the board were to accept that the skilled person is aware of the fact that collagen is naturally devoid of an ER retention sequence, the application as filed directs the skilled person either to the combination of the collagen alpha chain with the feature "*devoid of ER targeting sequence*" or to the combination with the feature devoid of both the ER targeting and retention sequences, but not to a combination with the feature "*devoid of ER retention sequence*" only.

Combination of the features "attached to a vacuole transit peptide" and "devoid of an ER retention sequence"

15. According to established case law, the content of an application is not to be considered to be a reservoir from which features pertaining to separate embodiments of the application can be combined in order to artificially create a particular embodiment. In the absence of any pointer to that particular combination, this combined selection of features does not, for the person skilled in the art, emerge clearly and unambiguously from the content of the application as filed (see Case Law of the Boards of Appeal, 8th edition, 2016, section II.E.1.4 and decisions cited therein).

16. As stated above, the application does not direct the skilled person to combine the feature "*exogenous polynucleotide sequence encoding at least one type of a collagen alpha chain*" with either the feature "*attached to a vacuole transit peptide*" or the feature "*devoid of an ER retention sequence*". The claimed combination of

features is therefore not directly and unambiguously disclosed in the application as filed.

17. Appellant I submitted that each of the features "*attached to a vacuole transit peptide*" and "*devoid of an ER retention sequence*" was individually disclosed in the application as filed and that the claimed combination of the features was understood by the skilled person to be a technical prerequisite to achieve targeting of the collagen alpha chain to the vacuole and was thus unambiguously and directly disclosed for the skilled person.

18. The board does not find this line of argument persuasive for the following reasons.

19. The application as filed explicitly discloses a different combination of technical features to achieve targeting of the collagen alpha chain to the vacuole. Thus, according to the application as filed, the ER targeting sequence normally present in collagen alpha chains is removed such that the collagen alpha chain is then devoid of an ER targeting sequence (see page 14, lines 10 to 16, examples 1 and 2, Table 1). To this collagen sequence - devoid of the native ER targeting sequence - the vacuole transit peptide sequence is fused (see also Figure 2). In other words, for vacuole targeting of the collagen alpha chain the explicit teaching of the application as filed is "*devoid of an ER targeting sequence*" not "*devoid of an ER retention sequence*".

20. Appellant I gave no reasons why the skilled person would ignore this explicit teaching in the application as filed and would understand that the collagen chain needed to be devoid of an ER retention sequence whilst

the ER targeting sequence was maintained, when the explicit teaching in the application as filed was that the native ER targeting sequence in the collagen alpha chain was removed.

21. Contrary to the submissions by appellant I, the subject-matter of claim 1 therefore does also not correspond to the examples. The claim is directed to constructs with the native ER targeting signal present, while according to the examples these sequences are deleted from the collagen alpha chain (see point 19 above).

22. As regards a basis for the combination of the features "*attached to a vacuole transit peptide*" and "*devoid of an ER retention sequence*" in respect of P4H, appellant I indicated the disclosure of the same features in relation to the collagen alpha chain and submitted that in the light of the passage on page 15, fourth paragraph the same modifications were to be made to both the collagen and the P4H protein.

23. However, since the board could not find a basis in the application as filed for the combination of the features "*attached to a vacuole transit peptide*" and "*devoid of an ER retention sequence*" with the collagen alpha chain, appellant I's argument cannot succeed, regardless of whether or not the skilled person would have understood from the passage on page 15 of the application as filed that the same modifications were to be made to both the collagen alpha chain and to P4H.

24. The board notes that in any case, also for P4H, the explicit teaching of the application as filed is to remove the ER targeting signal from both P4H subunits and - in addition - to remove the ER retention signal

from the P4H alpha subunit (see Example 1 and Table 1). Thus, removal of the ER targeting sequence, or of both the ER targeting and ER retention sequences, is disclosed in the application as filed in the context of P4H, but not removal of only the ER retention sequence.

25. The board concludes from the above that the subject-matter of claim 1 of auxiliary request 32 does not meet the requirements of Article 123(2) EPC. The sole claim request is thus not allowable.

26. In the absence of an allowable claim request the patent has to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated