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Datasheet for the decision of 9 April 2025

Case Number: T 1390/23 - 3.3.05

Application Number: 16704575.6

Publication Number: 3256573

IPC: B01D15/36, C12N7/00

Language of the proceedings: EN

Title of invention:
RECOMBINANT ADENO-ASSOCIATED VIRUS PARTICLE PURIFICATION WITH MULTIPLE-STEP ANION EXCHANGE CHROMATOGRAPHY

Patent Proprietor:
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Opponent:
D Young & Co LL

Headword:
rAAV purification/INSERM

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

Keyword:

Amendments - allowable (yes)
Inventive step - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
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Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 1390/23 - 3.3.05

D E C I S I O N
of Technical Board of Appeal 3.3.05
of 9 April 2025

Appellant: (Opponent)	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 25 May 2023 concerning maintenance of the European Patent No. 3256573 in amended form.**

Composition of the Board:

Chairman E. Bendl
Members: G. Glod
P. Guntz

Summary of Facts and Submissions

I. The appellant's (opponent's) appeal concerns the opposition division's decision finding that European patent No. 3 256 573 B1 in amended form based on the then main request met the requirements of the EPC.

II. The following documents are of relevance here.

D1: W. Qu et al., Current Pharmaceutical Biotechnology 16, 2015, 684-95
D1a: Evidence of the publication date of D1
D2: WO 2011/094198 A1
D4: M. Urabe et al., Molecular Therapy 13(4), April 2006, 823-8
D6: J. A. Ally et al., Human Gene Therapy 22, May 2011, 595-604
D8: Extract from "Ion Exchange Chromatography and Chromatofocusing: Principles and Methods", GE Healthcare, 2010, 1-58
D17: WO 02/12455 A1

III. With the statement setting out the grounds of appeal, the appellant submitted *inter alia* the following document.

D27: Declaration by Professor Robin Ali of 25 April 2023

IV. During oral proceedings of 9 April 2025 before the board, the respondent (patent proprietor) withdrew its main request and made then auxiliary request 1 its main request.

Claim 1 of this request reads as follows.

"*1. A method for obtaining purified recombinant Adeno-Associated Virus (rAAV) particles, comprising the steps of:*
a) performing a depth filtration of a starting material previously obtained from cells producing rAAV particles, said starting material comprising a cell lysate and/or a culture supernatant, whereby a rAAV-containing clarified composition is provided;
b) adjusting the pH of the rAAV-containing clarified composition at a basic pH so as to ensure optimal retention of the rAAV particles on the chromatographic support used at step c);
c) submitting the rAAV-containing clarified composition of step b) to a first step of anion-exchange chromatography on a chromatographic support, wherein elution is performed by using a linear salt gradient and wherein the rAAV-containing fraction is collected, whereby a first rAAV-enriched composition is provided;
d) submitting the first rAAV-enriched composition at least once to a second step of anion-exchange chromatography on a chromatographic support wherein elution is performed by using a linear salt gradient and wherein the rAAV-containing fraction is collected, whereby a second rAAV-enriched composition is provided;
e) submitting the second rAAV-enriched composition to a step of tangential flow filtration, whereby purified recombinant Adeno-Associated Virus (rAAV) particles are provided, wherein said method comprises neither an apatite chromatography nor a cation exchange chromatography step, and
wherein said rAAV particles belong to an AAV5 capsid serotype."

Claims 2 to 8 refer to claim 1.

V. The appellant's (opponent's) arguments relevant to the present decision can be summarised as follows.

The requirements of Article 123(2) EPC were not met. The disclaimer of both the cation-exchange chromatography step and the apatite chromatography step was not disclosed in the application as originally filed. In addition, claim 5 as originally filed required the pH to be adjusted at the end of step a), in contrast to current claim 1. The wording "cell lysate and a culture supernatant" originated from a more specific method than what was claimed now.

The requirements of Article 56 EPC were not met. When starting from D2 as the closest prior art, the objective problem could only be seen as the provision of an alternative method. The solution was obvious since pH adjustment to 8 and a linear salt gradient were known from D8, while the use of two anion-exchange chromatography steps was suggested in D2 (see, for example, the table at the top of page 16).

The subject-matter of claim 1 also lacked an inventive step when starting from D4 or D17 as the closest prior art.

VI. The respondent's arguments are reflected in the Reasons for the Decision given below.

VII. The appellant requests that the decision under appeal be set aside and that the European patent be revoked.

The respondent requests that the patent be maintained in amended form on the basis of the main request, submitted as auxiliary request 1 with the reply to the

appeal or on the basis of one of auxiliary requests 2 to 7, likewise filed with the reply to the appeal.

Reasons for the Decision

Main request

1. Article 123(2) EPC

The requirements of Article 123(2) EPC are met for the following reasons. Claim 1 is based on claims 1, 5 and 8; page 10, lines 16 to 19; and page 15, lines 1 to 3 of the application as originally filed.

1.1 The objection relating to "cell lysate *and*/or a culture supernatant" (emphasis added) was only raised at the appeal stage. Its admissibility under Article 12(4) and (6) RPBA does not need to be decided. In any case, it is not convincing.

The wording under debate is disclosed on page 11, line 15 of the application as originally filed. The skilled person directly and unambiguously recognises that in step a) a mixture of cell lysate and culture supernatant could be used for obtaining the clarified composition. Although the passage relates to an embodiment in which steps a), b), c) and d) are consecutive, it is evident to the skilled person that the same starting material could be used if the steps following step a) were arranged differently. Step a) is always performed independently of the sequence of the other steps and independently of the starting material being cell lysate, a culture supernatant or a mixture of both.

1.2 Claim 5 as originally filed specified that at the end of step a), the pH of the rAAV (recombinant adeno-associated virus)-containing clarified composition is adjusted to a basic pH. According to the appellant, the current wording of claim 1 did not exclude an additional step after step a) before adjusting the pH, thus it infringed the requirements of Article 123(2) EPC. The board is not convinced by this argument.

The wording of claim 5 as originally filed is also found on page 15, lines 1 to 3 of the application as filed. The skilled person reading this passage would understand that the clarified composition obtained in step a) should be treated such that its pH is changed to basic prior to putting it on the anion-exchange column. The example (page 27, lines 23 to 26), which also relates to rAAV5 in agreement with claim 1, confirms this understanding. Other buffer optimisation steps to ensure optimal retention are not excluded by the wording on page 15, lines 1 to 3 in combination with the teaching of the example and the disclosure on page 10, lines 11 to 15. The example only points to the correct general understanding that the pH of the buffer has to be changed to basic prior to the next chromatography step, which is independent of the buffers used. It is accepted that claim 1 does not exclude the presence of other chromatography steps in view of the wording "comprising", but claim 1 does not allow such a step between a) and b).

1.3 According to the disclosure in the application as filed on page 10, lines 16 to 17, the method does not comprise a cation-exchange chromatography step according to an embodiment. Page 10, lines 18 and 19 state that according to an embodiment, the method does not comprise an apatite chromatography step. The

skilled person reading these lines would understand that an embodiment is a preferred option. Not having a cation-exchange chromatography step is consequently preferred; the same applies to not having an apatite chromatography step. When looking at the example (page 27, line 13 to page 29, line 2), the skilled person realises that for the purification of rAAV5, neither a cation-exchange chromatography step nor an apatite chromatography step was used. Therefore, the skilled person understands that page 10, lines 16 to 19 teach for the case of rAAV5 that none of these steps should be present. No specific choices are necessary to arrive at this combination since only two chromatography steps are presented as preferably absent.

1.4 According to claim 8 as originally filed, AAV5 is the preferred serotype. Claim 1 is now limited accordingly. Therefore, this limitation is directly and unambiguously derivable from the application as filed.

2. Article 56 EPC

The requirements of Article 56 EPC are met.

2.1 The invention relates to the purification of rAAV particles.

2.2 It is undisputed that D2 is a suitable starting point for the discussion of inventive step. D2 discloses in claim 1 a method for purifying AAV vector particles. Claim 6 mentions AAV5.

The board agrees with the opposition division that D2 does not disclose the adjustment of the pH of the clarified composition to a basic pH, an additional anion-exchange chromatography step, and a linear salt

gradient in steps c) and d). The appellant's argument that D2 directly and unambiguously disclosed two sequential anion-exchange chromatography steps on pages 15 and 16, in particular in the table on page 16, is not convincing. It is true that the table on page 15 discloses an anion-exchange resin for AAV5 (Poros 50PI), but disclosure is lacking that two sequential anion-exchange chromatography steps are useful specifically for AAV5. The disclosure that in some cases two or more sequential chromatography steps may be useful does not specify these cases. There is no disclosure that the second step must also be an anion-exchange chromatography step if the first step was one. The disclosure is instead general in view of the statement: "*Sequential chromatography steps can use different resins performed sequentially in varying orders*". Example I (page 23) essentially shows again the same table as on page 15 but also fails to disclose in what situation more than one chromatography step should be applied and which steps should be used. Thus, the board sees no need to deviate from the opposition division's finding on this.

2.3 The problem to be solved by the patent is to provide a method in accordance with GMP (Good Manufacturing Practices) that is scalable for purifying rAAV5 particles with high purity and infectivity (paragraphs [0007] and [0010] of the patent, see also respondent's reply, paragraph bridging pages 9 and 10).

2.4 It is proposed to solve the problem by a method according to claim 1 characterised in that the pH of the rAAV-containing clarified composition is adjusted to a basic pH, the first rAAV-enriched composition is submitted at least once to a second step of anion-

exchange chromatography, and elution is performed by using a linear salt gradient.

2.5 It is accepted that example 1 of the patent provides evidence that the problem is successfully solved. The example illustrates a method according to claim 1 and shows that it is efficient for purifying clinical-grade rAAV5 preparations from clarified supernatants on a large scale and in good yields. D2 does not provide data for rAAV5 purification.

It is true that there are no comparative data for D2, but example 1 of the patent shows that the specific *combination* of steps allows solving the problem posed. Evidence is lacking that the same results would be obtained with the method of D2 when purifying rAAV5. D1, which was cited by the appellant in support of its argument that the problem was already solved in D2, indicates that anion-exchange chromatography allows obtaining high purity rAAV5 particles (page 691, table, line 4 (Poros PI)) but is completely silent about the results on a large scale and the yield in that case. Example 1 of D2 only states that it appears that the purification process is applicable to the purification of vectors based on most AAV serotypes (page 23, lines 10 to 12). There are no results in D2 for the purification of rAAV5. Therefore, it cannot be simply assumed that the problem is solved in D2. The problem does not need to be redefined in less ambitious terms.

2.6 There is no doubt that the individual distinguishing method steps are known to the skilled person. However, there is no teaching in the prior art that the specific *combination* of steps is beneficial for the purification of rAAV5 particles. The appellant's argument is based on the assumption that the problem to be solved was

merely the provision of an alternative method, which the board does not agree with in view of the lack of evidence.

It is true that, for example, D8 discloses linear gradient elution (page 42) and pH adjustment to pH 8 (page 35) as possible process steps, but there is no teaching that these steps in *combination* with two anionic chromatography steps would allow solving the posed problem.

This also applies to D6, which only deals with rAAV8.

As set out above, D1 discloses that anion-exchange chromatography allows obtaining high purity rAAV5 particles, but it also indicates that it is hard to establish an optimal method for all rAAV serotypes (page 687, last paragraph of chapter 3.3.1).

D4 does not deal with rAAV5. Even if it were accepted that it was conventional to apply techniques and protocols across different serotypes as set out in D27, there is still no teaching that it would be of benefit in the process of D2.

D2 generally discusses that two chromatography steps may be useful but does not provide any teaching of the benefits for rAAV5. Therefore, it does not point to the solution of the posed problem.

Consequently, the proposed solution is not obvious when starting from D2 as the closest prior art.

2.7 D4 was chosen as another starting point for inventive step. This objection had been part of the appellant's grounds for opposition (pages 16 to 19) and was not

withdrawn during opposition proceedings. D4 does not deal with rAAV5, and D4 does not disclose that the second rAAV-enriched composition obtained after the second anionic chromatography step is submitted to a step of tangential flow filtration. As indicated above (points 2.3 and 2.5), it is accepted that the problem to be solved is the one indicated in the patent. D4 does not solve this problem since it is silent about rAAV5.

Even if D27 were admitted into the appeal proceedings (Article 12(4) and (6) RPBA) and if it were accepted that it was conventional to apply techniques and protocols across different serotypes, there is still no teaching in D4 of a tangential flow filtration. So if the skilled person applied the technique described in D4 to rAAV5, there is no reason why they would add a tangential flow filtration step. It is accepted that such a tangential filtration step is known to the skilled person (e.g. D2 and D6), but the addition of such a step to the method of D4 when applying it to rAAV5 is based on hindsight.

Consequently, the proposed solution is not obvious when starting from D4 as the closest prior art.

2.8 D17 is another document used as the closest prior art by the appellant. D17 mentions AAV1, AAV2, AAV3, AAV4, AAV5 and AAVX7 as possible serotypes for rAAV (page 5, lines 23 to 30). The examples generally relate to rAAV but do not specify the serotype. Example 10 (page 21) discloses an anion-exchange chromatography step followed by heparin affinity chromatography. Tangential flow filtration is disclosed generally as an option for concentrating for storage and use (page 16, lines 19 to 22). However, there is no explicit and/or implicit

disclosure that this step is to be applied to the product of example 10. Therefore, the subject-matter of claim 1 differs from D17 in that D17 does not explicitly disclose a process for rAAV5 purification and in that D17 does not disclose a second anion-exchange step, elution using a linear salt gradient and tangential flow filtration. As indicated above (points 2.3 and 2.5), it is accepted that the problem to be solved is the one indicated in the patent. D17 does not solve this problem since there are no data on rAAV5.

Again, the proposed solution to the posed problem is not obvious. As indicated when starting from D2 as the closest prior art, the individual distinguishing method steps are known to the skilled person, but there is no teaching in the prior art that the specific combination of steps is beneficial for the purification of rAAV5 particles. The choice of a second anion-exchange step, elution from it using a linear salt gradient and subsequent tangential flow filtration are not taught to be beneficial for the purification of rAAV5 particles. Consequently, the proposed solution is also not obvious when starting from D17 as the closest prior art.

2.9 In summary, the subject-matter of claim 1, and of claims 2 to 8 depending on it, involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of the claims of the main request, filed as auxiliary request 1 with the reply to the appeal, and a description to be adapted.

The Registrar: The Chairman:

C. Vodz E. Bendl

Decision electronically authenticated