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Datasheet for the decision of 26 April 2022

Case Number: T 1203/19 - 3.3.08

Application Number: 10772050.0

Publication Number: 2428229

IPC: C12N15/861, A61K48/00, C12N9/26

Language of the proceedings: EN

Title of invention:
ONCOLYTIC ADENOVIRUSES FOR TREATING CANCER

Patent Proprietors:
Fundació Privada Institut D'investigació Biomèdica
Institut Català D'Oncologia

Opponent:
Hoffmann Eitle Patent- und Rechtsanwälte PartmbB

Headword:
Oncolytic adenoviruses/INSTITUT CATALA D'ONCOLOGIA

Relevant legal provisions:
EPC Art. 54, 56, 104(1), 112a(2)(c)
EPC R. 106

Keyword:
Second auxiliary request - novelty - (yes)
Inventive step - (yes)
Apportionment of costs - (no)
Objection under Rule 106 - under condition (dismissed)

Decisions cited:
G 0003/14, G 0002/21, R 0004/08, R 0014/11, T 0609/02, T 1437/07, T 1457/09

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Case Number: T 1203/19 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 26 April 2022

Appellants: (Patent Proprietors)	Fundació Privada Institut D'investigació Biomèdica Hospital Duran i Reynals, 3ª planta Gran Via de l´Hospitalet, 199 08908 Hospitalet de Llobregat Barcelona (ES) Institut Català D'Oncologia Gran Via s/n 199-203 08907 L'Hospitalet de Llobregat (ES)
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Respondent: (Opponent)	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastrasse 30 81925 München (DE)
Representative:	Ogle, James Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastrasse 30 81925 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 February 2019 revoking European patent No. 2428229 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	M. R. Vega Laso
	F. Bostedt

Summary of Facts and Submissions

I. The appeal lies from a decision of an opposition division posted on 5 February 2019 revoking the European patent No. 2 428 229 with the title "Oncolytic adenoviruses for treating cancer". The patent was granted from the European application No. 10772050.0 filed under the Patent Cooperation Treaty (PCT) and published as WO 2010/128182, which claimed the priority of an earlier Spanish application. In the present decision, references to the "application as filed" are to the translation of the application published as EP 2 428 229 A1.

II. The patent was opposed on the grounds for opposition under Article 100(a) in conjunction with Articles 54 and 56, and under Article 100(b) EPC.

III. In the decision posted on 5 February 2019, the opposition division found that the main request and auxiliary requests 1, 4, 5, 10 and 11 then on file lacked novelty over document (13), and that auxiliary requests 2, 3, 6, 7, 8, 9 and 12 to 16 lacked an inventive step. Auxiliary request 17 filed during the oral proceedings was not admitted. In the absence of a request which met the requirements of the EPC, the opposition division revoked the patent.

IV. The patent proprietors (appellants) filed an appeal and submitted a statement setting out the grounds of appeal including 12 sets of claims as main request and first to eleventh auxiliary

requests. The appellants filed also additional documentary and experimental evidence, as well as a copy of the letters filed by both parties in opposition proceedings.

V. Claims 1, 12, 13, 17 and 18 of the second auxiliary request read as follows:

"1. An oncolytic adenovirus comprising a sequence encoding a hyaluronidase enzyme inserted in its genome, wherein the enzyme sequence has the membrane-binding domain sequence eliminated resulting in a soluble enzyme.

12. The oncolytic adenovirus according to any of the claims 1-11, wherein the adenovirus has modifications in the capsid to increase its infectivity or to target a receptor present in a tumour cell.

13. The oncolytic adenovirus according to claim 12, wherein the modification of the capsid is the replacement of the KKTK heparan-sulphates binding domain present in the adenoviral fibre with the RGDK domain.

17. A pharmaceutical composition which comprises a therapeutically effective amount of the oncolytic adenovirus as defined in any of the claims 1-16, together with pharmaceutically acceptable carriers or excipients.

18. Use of the oncolytic adenovirus comprising a sequence encoding a hyaluronidase enzyme inserted in its genome for the manufacture of a medicament for the treatment of a cancer or a pre-malignant

state of cancer, in a mammal including a human."

Dependent claims 2 to 11 and 14 to 16 relate to various embodiments of the oncolytic adenovirus according to claim 1.

VI. The opponent (respondent) replied to the statement of grounds and filed further evidence.

VII. The parties were summoned to oral proceedings before the board. In a communication sent in preparation of the oral proceedings, the board drew attention to matters which seemed to be of special significance and expressed a provisional opinion on some of the issues raised by the parties in their submissions.

VIII. Oral proceedings were held by video conference on 26 April 2022. During the oral proceedings, the appellants withdrew their main request and first auxiliary request and requested that the patent be maintained on the basis of the second auxiliary request. The respondent filed via email a written objection under Rule 106 and Article 112a(2)(c) EPC as follows (emphasis in original):

"*Considering that the Board of Appeal decided to admit the Patentee's late-filed document D47, which relates to a technical effect based exclusively on post-filing evidence, and considering that the Respondent cannot yet know the actual full reasoning for the decision, purely as a precaution in case the information from D47 has in fact and in substance affected the Boards decision in finding an inventive step,* ***objection*** *in respect of a procedural defect is raised under*

Rule 106 and Art 112a(2)(c). If the information from D47 has in fact and in substance affected the Boards decision in finding an inventive step, the respondent's right to be heard under Art 113 EPC will have been violated due to the fact that proceedings were not stayed in view of pending referral G2/21 to the Enlarged Board of Appeal, considering that the law relating to such post-filing data relating a technical effect based exclusively on post- filing evidence is to be clarified and potentially developed by this referral, and full arguments taking into account the law of the Enlarged Board could be presented once the outcome of referral G2/21 is known."

IX. The following documents are referred to in this decision:

(3): S. Ganesh et al., June 2008, Clin. Cancer. Res, Vol. 14(12), pages 3933 to 3941;

(6): S. Guedan et al., July 2010, Molecular Therapy, Vol. 18, No. 7, pages 1275 to 1283;

(7): C.-O. Yun, 2006, Current Opinion on Molecular Therapeutics, Vol. 10(4), pages 356 to 361;

(8): A. Haseley et al., January 2009, Recent Pat CNS Drug Discov., Vol. 4(1), pages 1 to 13;

(9): J. J. Cody and J. Douglas, 2009, Cancer Gene Therapy, Vol. 16, pages 473 to 488;

(10): M. Bauzon and T. Hermiston, 2008, Current Opinion in Molecular Therapeutics, Vol. 10(4), pages 350 to 355;

(12): G. Frost, 2007, Expert Opin. Drug Deliv., Vol. 4(4), pages 1 to 14;

(13): WO 2005/018332, published 3 March 2005;

(14): WO 2004/078140, published 16 September 2004;

(16): WO 2006/091871, published 31 August 2006;

(17): N. Byo-Puxan et al., October 2009, Human Gene Therapy, Vol. 20, pages 1214 to 1221;

(19): U. Novak et al., 15 December 1999, Cancer Research, Vol. 59, pages 6246 to 6250;

(21): A. Rodriguez-Garcia et al., 15 March 2015, Clin Cancer Res., Vol. 21(6), pages 1406 to 1418;

(25): D. Liu et al., July 1996, Proc. Natl. Acad. Sci., Vol. 93, pages 7832 to 7837;

(26): P. Rooney and S. Kumar, 1993, Differentiation, Vol. 54, pages 1 to 9;

(27): Annex II, Experimental Report "Demonstration of an advantage of the administration of an oncolytic adenovirus expressing hyaluronidase over the co-administration of soluble hyaluronidase and an oncolytic adenovirus in terms of therapeutic efficacy, not dated;

(31): R. Stern, 2003, Glycobiology, Vol. 13, No. 12, pages 105R to 115R; and

(47): Internal Report VCNA-B2-96, "Assessment of the antitumoural efficacy of VCN-01 vs concomitant administration of ICOVIR15K and rHuPH20 after intratumoural administration in mice bearing A375-P tumours", dated 3 June 2019.

X. The submissions made by the appellants, as far as relevant to the present decision, were essentially as follows:

Article 54 EPC

Document (13) - Claims 1 and 18

Claim 1 was novel in view of document (13), which did not describe a soluble hyaluronidase. There was no evidence on file showing that hyaluronidases could only work in soluble form, but not when attached to the surface of vesicles derived from the lysed tumour cells.

The opposition division erred in finding that the subject-matter of present claim 18 lacked novelty in view of document (13). This document did not contain a single working example supported by experimental evidence showing a therapeutic effect of an oncolytic adenovirus expressing hyaluronidase. All the examples therein were prophetic examples. In Example 8, the sole "evidence" of a medical use, a non-adenoviral oncolytic vector and another non-oncolytic vector expressing collagenase were co-administered. Thus, it was not credible that an antitumour effect could be achieved.

At the priority date of document (13), the teaching of this document was not enabling. Documents (19), (25) and (26) reported pro-tumoral effects of hyaluronidase, particularly that hyaluronidase was related to tumour growth and progression, and angiogenesis. Thus, a person skilled in the art would not have considered that an oncolytic adenovirus expressing hyaluronidase could have antitumoural effect in the treatment of cancer. Document (31) showed that there were serious doubts, substantiated by verifiable facts, that an adenovirus expressing hyaluronidase had therapeutic effect.

Documents (14) and (16) – claim 1

Neither document (14) nor document (16) described an oncolytic adenovirus. Hence claim 1 was novel.

Article 56 EPC

Document (3) as the closest state of the art

Document (3) described co-administration of hyaluronidase enzyme together with the oncolytic adenovirus, whereas claim 1 required that a sequence encoding hyaluronidase was present in the adenoviral genome. The technical effect associated with this difference was an improved antitumour effect, particularly a statistically significant increase of tumour growth inhibition. This improvement was shown in documents (27) and (47). The problem to be solved was the provision of an improved oncolytic adenovirus suitable for cancer therapy. Example 6 and Figures 7 to 9 of the patent showed that the adenovirus of the invention

was effective in the treatment of cancer *in vivo* and, thus, solved the problem. The superior inhibition of tumour growth of the oncolytic adenovirus expressing hyaluronidase was an unexpected and surprising effect.

The skilled person had no incentive to insert a sequence encoding hyaluronidase into an oncolytic adenovirus and no expectation to obtain an improved antitumour effect. Document (3) taught away from the approach described in document (9). Hence, an inventive step had to be acknowledged.

Document (13) as the closest state of the art

Document (13) did not qualify as the closest state of the art because it was speculative and did not solve the problem of providing an improved oncolytic adenovirus suitable for cancer therapy. None of the examples in document (13) dealt with hyaluronidase.

Claim 13

Document (6), which is the closest prior art, described an oncolytic adenovirus ICOVIR17 having a RDG motif inserted into the HI loop of the knob adenoviral fibre and a KKTK heparan sulphates binding domain on the shaft of the adenoviral fibre, whereas in the adenovirus of claim 13 the latter motif was replaced by the motif RGDK. As shown in document (21), the technical effect of this difference was a greater therapeutic efficacy in the treatment of cancer. This effect was unexpected and surprising in view of a combination of document (6) with document (17). Hence, the

oncolytic adenovirus of claim 13 involved an inventive step.

Claim 18

For the same reasons as claim 1, the subject-matter of claim 18 involved an inventive step over document (13).

XI. The submissions made by the respondent, as far as relevant to the present decision, were as follows:

Article 54 EPC

Document (13) - Claims 1, 17 and 18

An oncolytic adenovirus as defined in claim 1 lacked novelty over document (13). The generic disclosure on pages 4 to 6 of document (13) alone was sufficiently specific, direct and unambiguous to destroy the novelty of the claimed subject-matter. In particular, an oncolytic adenovirus was directly and unambiguously individualized by the indicator "Most preferably" in the passage on page 5, lines 7 to 11 and in claim 7. Hyaluronidase was disclosed as a member of a single list provided, e.g., on page 6, line 10 and claim 2. While claim 7 did not depend on claim 2, there was no technical or other rational reason to believe that claims 2 and 7 were not combinable. It was beyond reasonable doubt that document (13) referred exclusively to soluble hyaluronidases because only soluble hyaluronidases were known to be suitable for medical use. Evidence was provided by paragraph [0014] of document (14).

Claim 17 also lacked novelty in view of document (13) which clearly disclosed a pharmaceutical composition in the passage from page 3, line 25 to page 4, line 11, and in claim 1.

Document (13) also destroyed the novelty of claim 18. While the document did not provide data showing that an oncolytic adenovirus encoding hyaluronidase could effectively treat cancer, there was no doubt that it was credible that an adenovirus can be used to treat cancer, because the treatment of cancer using oncolytic adenoviruses, including the relevant underlying therapeutic mechanism, was already well known in the art. The general concept of increasing the dispersion of viruses by degrading a component of the extracellular matrix with collagenase was rendered credible by document (13), and there was no concrete reason to doubt that this concept applied to hyaluronidase. Documents (19), (25) and (26) did not establish serious doubts about the enablement of the disclosure in document (13). In contrast, the later and much more relevant review article filed as document (31) showed that it was common general knowledge at the time document (13) became available that hyaluronidase can be used successfully in combination with other anticancer agents to treat cancer.

Documents (14) and (16) – claims 1, 4, 5, 7 and 16

The subject-matter of claim 1 lacked novelty also in view of documents (14) and (16) which were concerned with soluble hyaluronidase glycoproteins and their uses. In document (14) adenoviruses were singled out as "especially attractive vehicles",

also and in particular for therapeutic purposes. Oncolytic adenoviruses were also disclosed because the reference in paragraphs [0463] to [0466] to the "replication and spread" of the armed virus within a target tissue directly and unambiguously implied lysis and not only replication. Document (16) was also novelty-destroying as it disclosed subject-matter corresponding to that of document (14).

Article 56 EPC

Document (3) as the closest state of the art

In the decision under appeal, document (3) had been regarded as the closest prior art. The oncolytic adenovirus of claim 1 was different from the adenovirus described in document (3) in that it was "armed" with the hyaluronidase, i.e. it expressed the hyaluronidase from its genome. No technical effect associated with this difference had been shown. Document (27) was inadequate as evidence to support the alleged effect, and the experimental evidence in document (47), if admitted into the proceedings, was irrelevant because the claimed invention was obvious regardless of whether there was a technical effect.

Document (13) as the closest state of the art

Document (13) provided an at least equally promising starting point for the assessment of inventive step as it was concerned with the same purpose as the alleged invention. Whether the disclosure was "generic" was not a consideration

in this respect. There was no doubt that document (13) enabled the skilled person to modify an oncolytic adenovirus with a nucleic acid encoding a relevant enzyme intended to increase viral spread, including hyaluronidase. The closest exemplified embodiment in document (13) was an oncolytic adenovirus armed with MMP, as disclosed on page 15, lines 12 to 16; page 23, lines 25 to 30 and in Figure 5B.

The claimed subject-matter was obvious in view of document (13) alone or in combination with common general knowledge, because hyaluronidase had been directly implicated in the treatment of cancer (e.g., document (31)), and used in combination therapies to enhance the effect of oncolytic viruses, as described in document (8) (see page 12, second paragraph, last sentence). As it was shown in documents (8), (9) and (10), it was commonly known to engineer ("arm") oncolytic adenovirus to express therapeutically useful transgenes. It was also commonly known that agents which permeated and facilitated the spread of viral vectors include hyaluronidase.

Claim 13

The subject-matter of claim 13 was not entitled to priority. Document (6) was the closest prior art. The technical effect associated with mutation of the KKTK motif was that the adenovirus showed better *in vivo* antitumoural activity. However, this effect was not mentioned or derivable from the application but could be derived only from post-published document (21). Hence, the effect could not be used as a basis for formulating the

technical problem. In any event, a person skilled in the art starting from document (6) derived a concrete expectation of achieving the alleged advantage from document (17). Thus, the subject-matter of claim 13 was obvious over the combination of documents (6) and (17).

Claim 18

The reasons put forward in connection with claim 1 applied also to claim 18. Its subject-matter lacked an inventive step.

XII. The appellants requested that the decision under appeal be set aside and the patent be maintained based on the claims of the second auxiliary request, filed together with the statement setting out the grounds of appeal.

XIII. The respondent requested that the appeal be dismissed, and that the claims according to the 9th auxiliary request and the late-filed arguments and evidence submitted by the appellants with the statement setting out the grounds of appeal be held inadmissible. In the event that the appellants' late-filed arguments and evidence were admitted into the proceedings, the respondent requested admittance and consideration of documents (52) to (56) submitted with the reply to the statement of grounds of appeal. Furthermore, the respondent requested an apportionment of the costs resulting from the late filing of arguments and evidence by the appellants.

Reasons for the Decision

Second auxiliary request

Rule 80 and Articles 123(2)(3) and 84 EPC

1. In the decision under appeal, the opposition division found that the amendments introduced into the claims of the second auxiliary request complied with Rule 80 and Article 123(2)(3) EPC, and that, in view of the decision of the Enlarged Board of Appeal G 3/14 (OJ EPO 2015, A102, clarity objections could not be raised with respect to amended claim 1 (see section 4.1 of the decision under appeal). These findings were not contested in the appeal proceedings. The board does not see any reason to raise any issues in this respect of its own motion.

Article 83 EPC

2. Sufficiency of disclosure was not discussed in the decision under appeal, and in appeal proceedings the respondent did not raise any objection under Article 83 EPC.

Article 54 EPC

Document (13)

Claim 1

3. In the decision under appeal, document (13) was considered not to be prejudicial to the novelty of the subject-matter of claim 1 of the second auxiliary request, because in the opposition

division's view this document did not describe a soluble hyaluronidase enzyme. Moreover, the opposition division held that there was no evidence on file that only soluble hyaluronidase could be meant in document (13) (see section 4.2.3 of the decision).

4. The board shares the opposition division's view that a person skilled in the art cannot derive directly and unambiguously from document (13) an oncolytic adenovirus comprising a sequence which encodes a soluble hyaluronidase enzyme.

5. The respondent relied on paragraph [0014] of document (14) as evidence that nothing but a soluble hyaluronidase could be envisaged for the intended medical use. The passage of document (14) quoted by the respondent in its submission relates to the clinical use of preparations containing a soluble hyaluronidase enzyme extracted from bovine testes in aqueous solution for subcutaneous injection (Wydase® or Hyalase®).

6. The known clinical uses of these hyaluronidase preparations are however unrelated to the envisaged use of the microorganisms (e.g., virus or bacteria) described in document (13), which are genetically modified to contain a sequence encoding a protein advantageous for migration of the microorganism throughout a tumour. A skilled person reading document (13) understands that the purpose of including the coding sequence in the virus or bacteria described in this document is that the protein be produced *in situ* (i.e., in the tumour) by expression of the coding sequence,

rather than being delivered by injection. Hence, contrary to respondent's view, the board is not persuaded that a skilled person derives from the technical content of document (13) a compelling reason for eliminating the sequence encoding the membrane-binding domain of the hyaluronidase enzyme to render a soluble enzyme.

7. Consequently, the subject-matter of claim 1 is considered to be novel over document (13).

Claim 17

8. Claim 17, which is directed to a pharmaceutical composition comprising the oncolytic adenovirus, refers to claims 1 to 16 and thus includes the limiting feature that the encoded hyaluronidase enzyme lacks the membrane-binding domain. For the reasons given above in connection with claim 1, also the subject-matter of claim 17 is considered to be novel over document (13).

Claim 18

9. Unlike claims 1 to 17, claim 18, which is directed to the therapeutic use of an oncolytic adenovirus, does not include the limitation that the encoded hyaluronidase enzyme has the membrane-binding domain eliminated (see section V. above). While in the decision under appeal novelty was not discussed with respect to claim 18 of the second auxiliary request, the opposition division found that the subject-matter of the identical claim 1 of the fourth auxiliary request lacked novelty in view of document (13) as a whole, and in

particular of claim 23 and page 40 of that document (see section 5.2.3 of the decision under appeal).

10. Document (13), a patent application filed under the PCT, discloses a method of treating cancer in a mammal by administering one or more genetically engineered microorganisms which comprise a nucleic acid encoding a protein that breaks down the interstitial matrix or targets the tumour vasculature, said administering being for a time and in an amount sufficient to destroy, slow, or arrest the cancer (see claim 17). A preferred microorganism is described as an adenovirus which comprises a mutation in the E1A CR-2 gene, the mutation resulting in the inactivation of the gene (see claim 23, which depends on claim 17, and page 5, lines 7 to 11). Document (13) also contains a list of various proteins that may break down the interstitial matrix or target the tumour vasculature, including hyaluronidase (see, e.g., the passage on page 4, lines 23 to 30 under the heading "Summary of the Invention").

11. Pursuant to established case law of the Boards of Appeal, the content of a document comprised in the state of the art is prejudicial to the novelty of the claimed subject-matter only if the technical teaching of the document is reproducible, i.e., if it can be carried out by a person skilled in the art (see decision T 1437/07 of 26 October 2009, points 25 and 26 of the Reasons). If the claimed subject-matter pertains to a use in connection with a medical treatment, for the requirement of reproducibility to be regarded as fulfilled it is necessary that the disclosure in the prior art

document is such as to make it credible that the therapeutic effect on which the method of treatment relies can be achieved (see decision T 1457/09 of 17 January 2014, point 36 of the Reasons which refers to decision T 609/02 of 27 October 2004, point 9 of the Reasons).

12. The therapeutic application of the present patent is based on the finding that the expression of a sequence encoding a hyaluronidase enzyme inserted in the genome of an oncolytic adenovirus improves the distribution of the virus through the tumour mass, increases its antitumour efficacy and induces tumour regression (see paragraphs [0017] and [0060] to [0064] and Figures 7 to 9 of the patent).

13. Document (13) does not include any experimental results whatsoever showing expression of the hyaluronidase sequence in tumour cells infected with the described adenovirus, either *in vitro* or *in vivo*, nor improved distribution of the described genetically engineered adenovirus within a tumour or tumour regression induced by administering the adenovirus. As a matter of fact, none of the examples of document (13) involves the use of an adenovirus, let alone an oncolytic adenovirus comprising a sequence which encodes a hyaluronase enzyme. Hence, document (13) itself does not provide anything of substance that makes it credible that the genetically engineered adenovirus described therein is in fact suitable for the treatment of cancer.

14. In the decision under appeal, the opposition division stated that they did not see any

prejudice in the art to the use of hyaluronidases. In their view, the cited prior art, in particular documents (19), (25) and (26) on the one hand, and document (3) on the other hand, "*goes in different directions*", while document (31) was regarded as "*controversial*" (see section 5.2.3 of the decision).

15. In the board's view, in the absence of relevant experimental data in the document which may support a therapeutic effect, the **common general knowledge** of the skilled person at the publication date of document (13) becomes highly relevant. Therefore, only if – in the light of this common general knowledge – it was credible that the genetically engineered adenovirus described in document (13), which comprises a sequence encoding a hyaluronidase, was suitable for treating cancer in a mammal, it can be concluded that the skilled person derives this technical teaching from document (13). The board considers that – in view of the common general knowledge set out below - the skilled person would have had serious doubts in this regard and that, therefore, this technical teaching cannot be seen as being derivable from document (13).

16. Unlike the opposition division, the board does not consider the content of document (3) to be common general knowledge at the publication date of document (13), because document (3) was published more than three years later. As regards documents (19), (25) and (26) cited by the appellants to support their argument that expression of hyaluronidase in a tumour has been associated with tumour growth and metastasis or with induction of

angiogenesis, the respondent argued that the content of these documents cannot be regarded as common general knowledge of the skilled person, and that only the content of document (31), a review article on hyaluronan catabolism and hyaluronidases, qualified as such.

17. However, document (26) is a short review article published before the publication date of document (13); hence, contrary to respondent's view the content of document (26) is to be regarded as common general knowledge of the skilled person at the relevant date. This document reports on various observations which, when taken together, are said to imply that hyaluronan breakdown plays a role in tumour metastasis (see page 3, right-hand column, second full paragraph under the heading "Development and tumour formation"). Hyaluronan breakdown is effected by the hyaluronidase enzyme.

18. As regards document (31), it is apparent from the chapter under the heading "The cancer conundrum" on page 111R that there were many unanswered questions on the role of hyaluronidase enzymes regarding tumour progression and angiogenesis. It is stated in this chapter that hyaluronidases had been added to anticancer drugs in chemotherapy regimes, on the assumption that they may enhance the penetration of the drugs and decrease the turgor of malignant tissues, and that based on the results of experimental tumour studies, hyaluronidase enzymes may themselves have intrinsic anticancer activities (see second and third paragraph of the chapter). However, the clinical data are said to be inconsistent because

in some studies increased levels of hyaluronidase enzyme were shown to correlate with tumour progression, while in other studies the progression was correlated with increased levels of hyaluronan synthesis (see page 111R, right-hand column, first full paragraph). Document (31) also indicates that the action of the Hyal 2 hyaluronidase provides hyaluronan fragments of intermediate molecular weight which induce the angiogenesis required for malignancy progression (see page 111R, right-hand column, third full paragraph). In sum, the picture that emerges from document (31) regarding the role of hyaluronidases and hyaluronan catabolism in tumour progression is far from clear, in fact a "conundrum".

19. In view of the above, the board is not persuaded that a person skilled in the art, in the absence of relevant experimental data which may support a therapeutic effect, and in the light of the common general knowledge as described in documents (26) and (31), may consider the genetically engineered adenovirus described in document (13) to be suitable for the treatment of cancer in a mammal.

20. Consequently, document (13) does not destroy the novelty of the subject-matter of claim 18.

Documents (14) and (16) – Claims 1, 4, 5, 7 and 16

21. The objection of lack of novelty in view of documents (14) and (16) raised in the notice of opposition was not discussed in the decision under appeal but was maintained by the respondent in the appeal proceedings.

22. Document (14) describes human soluble hyaluronidase glycoproteins, pharmaceutical compositions comprising these glycoproteins, and methods for their recombinant expression in a mammalian system. The passage starting at paragraph [0320] describes various methods of treatment based on administering either the soluble hyaluronidase glycoprotein or a nucleic acid including a nucleotide sequence which encodes the hyaluronidase polypeptide or functional domains or derivatives thereof. In particular, paragraphs [0338] ff. describe the use of the nucleic acid in gene therapy.

23. To substantiate its objection of lack of novelty in view of document (14), the respondent relied on a combination of paragraphs [0341], [0343], [0465] and [0466], which allegedly describe all the features of claim 1.

24. Contrary to the respondent's view, the board is unable to find in document (14) a direct and unambiguous disclosure of an oncolytic adenovirus having the features specified in claim 1. This feature of the claimed adenovirus cannot be considered inherent in the fact that adenoviruses may be able to replicate in cancer cells because viral replication does not necessarily result in lysis of the host cell. Hence, the novelty objection in view of document (14) fails. The same conclusion is reached with respect to document (16) in which the disclosure with respect to adenoviruses is equivalent to that of document (14).

Article 56 EPC

Claim 1

Document (3) as the closest state of the art

25. Document (3), which the opposition division regarded as the closest state of the art for the assessment of inventive step (see section 4.4.1 of the decision under appeal), describes the co-administration of recombinant soluble hyaluronidase enzyme (rHuPH20) and oncolytic adenovirus to tumour-bearing mice by intratumoural injection, with the purpose of improving the spread of the virus throughout the tumour and the antitumour efficacy of the therapy.

26. The difference between the oncolytic adenovirus described in document (3) and the claimed adenovirus is that the latter comprises a sequence encoding a soluble hyaluronidase enzyme inserted in the genome.

27. The respondent alleged that neither a technical effect associated with this difference, nor a technical improvement can be derived from the patent. The board disagrees. In paragraphs [0011] and [0015] to [0017] of the patent, the differences between the claimed adenovirus and the adenovirus described in document (3) are discussed in detail. In particular, the patent discloses:

"*The present invention allows the expression of hyaluronidase at the site and moment that viral replication takes place. This expression of hyaluronidase improves the distribution of the virus through the tumour mass and increases its*

antitumour potency. It is feasible to administer adjusted doses, non-toxic for the animal, with great efficacy for the treatment." (paragraph [0017])

"[...], *with the adenovirus of the invention the administered doses are smaller: in Ganesh et al. (supra)* [document (3) in the present proceedings] *four intratumour injections of* $1x10^{10}$ *viral particles are administered, whereas in the present invention a single endovenous dose of* $2x10^{9}$ *viral particles is administered. This means a dose reduction of 20 times and the advantage of being a unique dose. In their approach, Ganesh et al. administer hyaluronidase intratumorally every other day throughout the experiment. In addition adenovirus also is administered intratumourally at the beginning of the treatment. This intratumour administration of virus and hyaluronidase it is hardly applicable to the clinic because most tumours are not accessible for an intratumoural administration. Presumably the soluble coadministration of hyaluronidase and adenovirus was not made by systemic route because the probability that both components reach together the scattered tumour cells in the organism is low.*" (paragraph [0016])

"*As it is described in the examples, the intratumoural in vivo administration of the oncolytic adenovirus of the invention improves the antitumour effect with respect to an adenovirus control without the inserted hyaluronidase (see FIG. 7). Of note, when the oncolytic adenovirus of the invention is injected endovenously (see FIG. 8 and FIG. 9) and, in comparison to the results*

presented in figure 2 of the manuscript of Ganesh et al., a much greater tumour growth inhibition is observed with the present invention adenovirus. This indicates that the treatment of the invention is more effective. The tumours of the mice injected with the oncolytic adenovirus of the invention (ICOVIR17) show very extensive necrotic areas, areas with less viable cells, and large and numerous centers of virus replication, in comparison with the tumours injected with the adenovirus control, ICOVIR15." [paragraph [0015])

"*In these studies* [document (3)] *oncolytic adenoviruses are administered in four intratumoural injections and hyaluronidase is administered intratumourally every other day during all the treatment. This regimen of administration has little application to patients because most of the tumours are inaccessible to be injected intratumourally. The patients with scattered disease (metastasis) could not benefit from the treatment proposed by Ganesh and collaborators.*" (paragraph [0011])

Hence, regarding the technical effect and the advantages associated with the oncolytic adenovirus of claim 1 the patent speaks for itself.

28. In the board's view, the technical effect associated with the sequence encoding a soluble hyaluronidase enzyme inserted in the genome of the oncolytic adenovirus is the delivery of hyaluronidase enzyme *in situ* as oncolysis progresses through the tumour (see paragraph [0017] of the patent). In view of the numerous advantages of the claimed adenovirus over that

described in document (3) (see the preceding paragraph), the board is persuaded that the problem of providing an improved oncolytic adenovirus is solved by the claimed invention. Thus, the comparative data submitted by the appellants as documents (27) and (47) do not need to be considered for this decision.

29. The sole remaining question is whether the claimed subject-matter was obvious to a person skilled in the art.

30. In the opposition division's view, from document (3) alone or in combination with document (9) "... *there was a strong incentive for the skilled person to introduce the transgene into the adenovirus*" because, purportedly, systemic administration is more desirable in cancer therapy than intratumoural administration.

31. However, the statements in the third paragraph of the "Discussion" chapter of document (3) contradict the opposition division's view. It is stated in this passage that:

"*...hyaluronidase coinjection has the advantage of not requiring manipulation and can therefore be added to different viruses. In addition, by knowing the half-life of hyaluronidase, one has control over the amount of enzyme delivered to the tumor. In contrast, viruses expressing relaxin will produce relaxin as long as they replicate within the tumor cells, which might differ between tumors.*"

32. In the light of the common general knowledge (see, e.g., document (26) discussed in paragraph 17 above) and the statements in the introduction of document (3) pointing to a possible role of hyaluronan processing enzymes (i.e. hyaluronidases) in promoting growth and vascularization of tumours in mice (see page 3934, left-hand column, first full paragraph), the skilled person derives from the second sentence in the passage quoted above that controlling the amount of hyaluronidase enzyme delivered to the tumour may be important if deleterious effects, e.g. increased metastasis or vascularization of the tumour, are to be avoided. Further, from the last sentence of the passage quoted above, the skilled person becomes aware of the fact that a strict control over the amount of protein delivered to the tumour is not feasible if the protein is expressed from a sequence inserted in the viral genome, because the amount of protein produced will vary depending on the extent of viral replication in the tumour cells. The passage of document (9) to which the opposition division referred confirms that "... *the input dose of transgene is amplified by replication of the virus*" (see page 474, last sentence of the paragraph under the heading "Rationale for armed CRAds"). This applies also to the amount of protein encoded by the transgene.

33. Hence, unlike the opposition division the board does not regard the statements in document (3), either alone or in combination with the cited passage of document (9), as a motivation to deliver hyaluronidase enzyme to a tumour by expressing a sequence encoding the enzyme inserted

in the genome of an oncolytic adenovirus, but rather as clear hints against such an approach.

34. The respondent pointed to documents (8), (9) and (10) in support of its argument that the approach of engineering ("arming") a virus to express genes considered useful for the intended therapy with the objective of increasing therapeutic efficacy was commonly known in the art, and had been already applied to express relaxin, a peptide hormone that downregulates expression of collagen and upregulates expression of metalloproteinases, in a tumour.

35. It is undisputed that this approach formed part of the common general knowledge of the person skilled in the art at the priority date. In principle, the skilled person could consider applying it to increase the therapeutic efficacy of an oncolytic adenovirus. However, under the circumstances of the present case, in particular taking into account the skilled person's awareness of possible deleterious effects of uncontrolled (over)expression of hyaluronidase in a tumour, the board is not persuaded that the skilled person would try this.

36. The respondent contended that the skilled person would combine the teachings of document (3) with those of documents (14) and (16) and thus arrive at the claimed invention. Documents (14) and (16) relate to the characterization of soluble forms of the human PH-20 hyaluronidase glycoprotein and provide nucleic acids useful for the recombinant production of the soluble glycoproteins in a mammalian expression system (see paragraph [0019]

in document (14) and paragraph [0018] in document (16)). While various uses of the described soluble hyaluronidases, *inter alia*, the use in gene therapy, are described at a theoretical level therein, these documents do not provide any piece of information that would help the skilled person to overcome his/her concerns regarding the (over)expression of hyaluronidase in a tumour.

37. For these reasons, the board concludes that it was not obvious to a skilled person, starting from document (3) and in view of either the common general knowledge or the content of documents (14) and (16), to arrive at the subject-matter of claim 1.

Document (13) as the closest state of the art

38. The opposition division held that the generic disclosure of document (13) cannot be regarded as the most promising starting point for a proper assessment of inventive step applying the problem-solution approach. This finding was contested by the respondent.

39. With the aim of improving viral and bacterial based anti-cancer therapies that can both target neoplastic cells specifically and be effectively distributed throughout the tumour (see page 3, lines 19 to 21), document (13) generally teaches genetically modified microorganisms, e.g. viral vectors, that express a nucleic acid encoding a protein advantageous for migration of the microorganism through a tumour, in particular a protein that breaks down interstitial matrix or

targets tumour vasculature. The recombinant viral vectors can be injected in a tumour as a mixture together with an oncolytic viral vector (see Example 8 "Co-injection of a recombinant vector expressing collagenase and an oncolytic viral vector") or, in one example, a cDNA encoding a protein that targets the interstitial matrix or the tumour vasculature (e.g. MMP or relaxin) is inserted into a tumour cell-selective replication competent vector obtained by modifying the wild-type adenoviral genome via a deletion in the E1A CR-2 gene (see paragraph bridging pages 23 and 24, and Figure 5B). This embodiment corresponds to Example 9 on page 53, which reads:

"*To generate an oncolytic vector expressing collagenase, the collagenase cDNA is directly inserted into the oncolytic vector genome. The recombinant oncolytic vector is produced and the experiments described in Example 8 above are used to determine if the expression of collagenase improves the effectiveness of the oncolytic virus*".

No experimental results showing anti-cancer efficacy are provided in document (13), either for this particular embodiment or for any other viral vector.

40. As examples of proteins that may break down the interstitial matrix or target the tumour vasculature, document (13) provides a list which includes functionally defined proteins (e.g. a protein that increases extracellular matrix turnover) and specific proteins well known in the art, e.g. relaxin, collagenase and hyaluronidase

(see, e.g., page 4, lines 23 to 30).

41. In the respondent's view, the skilled person was particularly motivated to use hyaluronidase in an oncolytic vector because, as shown in document (31), it was common general knowledge that this enzyme had been directly implicated in the treatment of cancer. The respondent also referred to document (8), in particular the passage on page 12, second paragraph, last sentence which allegedly provided a link between MMP and hyaluronidase, thus providing a general motivation to use hyaluronidase "*in conjunction*" with oncolytic virus for the treatment of tumours.

42. These arguments are not persuasive. The wording "*in conjunction*" in the passage of document (8) cited by the respondent means "co-administered" or "co-injected", as apparent from reference [109], which corresponds to document (3) in the present proceedings. While document (31) (see observations in connection with the novelty of claim 18 in paragraphs 18 and 19 above) describes that hyaluronidase enzyme is co-injected with anticancer drugs in chemotherapy regimes, it does not provide a motivation to express a soluble hyaluronidase sequence inserted in a oncolytic adenovirus. On the contrary, this document makes the skilled person aware of experiments showing that increased levels of hyaluronidase enzyme correlate with tumour progression. As stated in connection with document (3) as the closest state of the art, the risk of inducing tumour progression or metastasis (see document (26), page 3, right-hand column, second full paragraph) if hyaluronidase is expressed in large amounts in

a tumour would deter the cautious and conservative skilled person from trying to express soluble hyaluronidase enzyme from a sequence inserted in an oncolytic adenovirus. As stated above, documents (14) and (16) do not provide the skilled person with any useful information in this respect. Nor does document (12) which merely describes that human soluble hyaluronidase administered by subcutaneous injection increased the dispersion of particles of different sizes, including adenoviruses (see page 8, left-hand column, third full paragraph).

43. Summarising the above, the board is not persuaded that the subject-matter of claim 1 was obvious to a skilled person from a combination of document (13) and the common general knowledge as described in documents (8) and (31), or the content of any of documents (14), (16) or (12). Hence, an inventive step is acknowledged.

Claim 13

44. The appellants did not dispute that the priority of the earlier Spanish application cannot be validly claimed for the subject-matter of claim 13 and that, consequently, documents (6) and (17) are part of the state of the art relevant to the assessment of inventive step.

45. Undisputedly, document (6), which is a scientific article authored by the inventors of the present patent and published online in the priority interval, is the closest state of the art because it is directed to the same purpose and requires the minimum of structural modifications to arrive

at the oncolytic adenovirus of claim 13.

46. The difference between the adenovirus as defined in claim 13 and the ICOVIR17 adenovirus described in document (6) is that in the latter the tripeptide RGD is inserted into the HI loop of the knob adenoviral fibre, whereas claim 13 specifies that the motif KKTK, which is located in the shaft of the adenoviral fibre, is replaced by the motif RGDK.

47. The subject of dispute between the parties was whether the technical effect associated with the distinguishing features specified in claim 13 is derivable from the application as filed. In the board's view, the passage on page 5, lines 55 to 58 of the application as filed provides a clear indication of the technical effect underlying the subject-matter of claim 14, namely increased infectivity and target cell specificity of the oncolytic adenovirus ("...*to increase its infectivity or to direct it better to the target cell*").

48. The technical problem to be solved starting from document (6) is thus the provision of an oncolytic adenovirus with improved antitumour efficacy. As shown in post-published document (21), an adenovirus with the features of claim 13 (VCN-01) shows improved antitumour activity compared to the adenovirus described in document (6). This has not been disputed by the respondent. Hence, the problem is solved by the oncolytic adenovirus of claim 13.

49. It remains to be assessed whether this solution was obvious. The respondent contended that document (17), which is also a publication of the inventors, describes a mutation of the KKTK heparin sulfate-binding domain of the fibre shaft to GATK which results in liver transduction detargeting. It is stated in this document that, similar to RGD at the HI-loop, RGD at this new shaft location efficiently enhances the infectivity of adenovirus (see Abstract). In the respondent's view, it was obvious to a person skilled in the art to try to replace the mutation described in document (6) by that described in document (17), with a reasonable expectation of achieving an improved antitumour efficacy.

50. This line of argument is tainted with the hindsight knowledge of the teaching of claim 13 of the patent. In the board's judgement, a person skilled in the art seeking to improve the antitumour efficacy of the adenovirus described in document (6) does not derive from this document any motivation to modify a domain in the adenovirus fibre.

51. The respondent alleged that a motivation was found in the passage bridging the left- and right-hand column of document (6). In this passage, the toxicity displayed by the ICOVIR17 and ICOVIR15 adenoviruses (with and without sequence encoding a hyaluronidase, respectively) after systemic administration in hamsters was studied. Slightly reduced body weight and a modest increase in AST and ALT levels were observed, but there were no significant differences between animals treated with either adenovirus. The authors concluded from

these results that hyaluronidase expression "... *did not significantly increase toxicity caused by an oncolytic adenovirus*".

52. In the board's view, the skilled person does not derive from these statements either a substantial toxicity problem associated with the adenoviruses described in document (6), or a link between the observed toxicity profile and particular domains in the adenovirus fibre. Absent a hint in document (6), it was not obvious to the skilled person to introduce modifications in the fibre shaft of the ICOVIR17 adenovirus.

53. Thus, an inventive step is acknowledged for the subject-matter of claim 13.

Claim 18

54. The respondent based an objection of lack of inventive step on document (13) as the closest state of the art in combination with documents (7), (8) or (12).

55. As stated above in connection with novelty, document (13) is not considered to be enabling for the use of the oncolytic adenovirus as defined in claim 1 for the treatment of cancer. If, as the respondent contended, the problem to be solved starting from this document were to provide an adequate treatment for cancer, the statements in document (8) (see page 12, last sentence of the second paragraph) would not suggest to the skilled person the use of an oncolytic adenovirus comprising a sequence which encodes a hyaluronidase, but rather the co-administration of

an oncolytic adenovirus and hyaluronidase enzyme in the tumour. As stated above, the wording "*in conjunction*" in that passage means "co-administered" or "co-injected" (see reference [109] which corresponds to document (3) in the present proceedings).

56. The passage on page 357, right-hand column of document (7) cited by the respondent as common general knowledge, refers to a study in which pre-treatment of rat muscle with hyaluronidase enzyme enhanced to increase diffusion of recombinant adeno-associated virus. This approach is equivalent to the approach of co-administration, the difference being that the hyaluronidase enzyme is administered before administration of the virus. As stated above, document (12) merely describes administering human soluble hyaluronidase administered by subcutaneous injection.

57. It follows from the above that the subject-matter of claim 18 is not obvious to a person skilled in the art in view of document (13) combined with common general knowledge. Hence, inventive step is acknowledged.

Request for apportionment of costs (Article 104(1) EPC)

58. The respondent requested apportionment of costs for the excess costs incurred by studying appellants' new arguments and evidence and by preparing a response thereto. Contrary to respondent's view, the board does not see in appellants' behaviour in appeal proceedings any

abuse of procedure. It is a normal behaviour of an appellant to request that new arguments and evidence addressing issues raised in the adverse decision be admitted into the proceedings. Whether or not the new submissions are admitted into the proceedings is however at the discretion of the board.

59. Further, the respondent requested apportionment of costs in case of a remittal due to the introduction of new arguments or documents at a late stage of the appeal proceedings. Except for document (47), which was admitted into the proceedings but is of no relevance for the reasons given in the present decision (see point 28, above), no other new arguments or documents were introduced into the proceedings. The case is remitted only for adaptation of the description. Thus, the request is void.

60. Hence, the apportionment of costs requested by the respondent is not justified.

Objection under Rule 106 EPC

61. During the oral proceedings, the respondent filed a written objection under Rule 106 and Article 112a(2)(c) EPC in which it made explicit reference to a fundamental violation of Article 113 EPC (see section VIII above).

62. At the point in time when the objection was made, i.e. in the oral proceedings, it was conditional. Specifically, the objection was made under the condition that a certain procedural defect may occur in the future, namely that the board's

reasoning for the finding on inventive step in the written decision may be based on the content of post-filed document (47), even though the board, by not staying the proceedings in view of the referral G 2/21 then pending before the Enlarged Board of Appeal, deprived the respondent of the opportunity to present full arguments taking into account the outcome of the referral. The objection thus pertained to an alleged procedural defect that had not yet arisen in the proceedings.

63. As the Enlarged Board has consistently held, the requirement pursuant to Rule 106 EPC to raise an objection should enable the board confronted with the objection to react immediately and appropriately by either removing the cause of the objection or, as provided in Rule 106 EPC, by dismissing it (R 4/08 of 20 March 2009, point 2.1 of the reasons; R 14/11 of 5 July 2012, points 2.5 and 2.6 with further references). In the present case, the cause for the objection raised by the respondent at the oral proceedings had yet to occur. Hence, respondent's objection was misplaced and the board had no other option than to dismiss it.

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 on the basis of claims 1 to 18 of the second auxiliary request filed with the statement setting out the grounds of appeal, and a description to be adapted.**

3. **The request for apportionment of costs is refused.**

The Registrar: On behalf of the Chair (according to Art. 8(3) RPBA 2020):

L. Malécot-Grob F. Bostedt

Decision electronically authenticated