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Datasheet for the decision of 11 December 2014

Case Number: T 0995/10 - 3.3.04

Application Number: 98949797.9

Publication Number: 1032269

IPC: A01N63/00, A61K35/76, C12N7/00, C12N7/02

Language of the proceedings: EN

Title of invention:
Treatment of neoplasms with interferon-sensitive, clonal viruses

Patent Proprietor:
Wellstat Biologics Corporation

Opponent:
Bayer Pharma Aktiengesellschaft

Headword:
Clonal RNA virus/WELLSTAT BIOLOGICS

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:

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Beschwerdekammern
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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 0995/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 11 December 2014

Appellant: (Opponent)	Bayer Pharma Aktiengesellschaft Müllerstrasse 178 13353 Berlin (DE)
Representative:	Weiss, Wolfgang Weickmann & Weickmann Patentanwälte Richard-Strauss-Strasse 80 81679 München (DE)
Respondent: (Patent Proprietor)	Wellstat Biologics Corporation 930 Clopper Road Gaithersburg, MD 20878 (US)
Representative:	MacLean, Martin Robert Mathys & Squire LLP The Shard 32 London Bridge Street London SE1 9SG (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 19 April 2010 rejecting the opposition filed against European patent No. 1032269 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	R. Morawetz
	M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeal of the opponent (hereafter "appellant") lies against the decision of the opposition division rejecting the opposition filed against European patent No. 1 032 269.

II. The patent at issue has the title "Treatment of neoplasms with interferon-sensitive, clonal viruses".

Claim 1 as granted reads as follows:

"1. Use of an interferon-sensitive, replication-competent clonal RNA virus for the manufacture of a medicament for treating a neoplasm in a mammal."

III. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC).

IV. The opposition division decided that the subject-matter of the claims as granted was novel and involved an inventive step.

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

D1 WO 94/25627

D4 Daniel M.D. and R.P. Hanson, Avian diseases (1968), vol. 12, pages 434-440

D11 Newcastle disease (1988), Kluwer Academic Publishers, edited by D.J. Alexander; pages 113-130 (Chapter 7) by R.P. Hanson

D12 Spradbrow P.B., Epidemiology of

newcastle disease and the economics of its control. In: Poultry as a tool in poverty eradication and promotion of gender equality- Proceedings of a workshop, pages 1-6

D14 Technical information, submitted by the respondent with letter dated 14 July 2005

VI. With its statement of grounds of appeal the appellant submitted arguments why the subject-matter of the claims as granted lacked novelty and inventive step.

VII. In response the patent proprietor (hereafter "respondent") maintained the claims as granted as main (sole) request and provided arguments to the effect that the claimed subject-matter was novel and involved an inventive step.

VIII. The parties were summoned to oral proceedings to be held on 11 December 2014. The board expressed its preliminary view in a communication pursuant to Article 15(1) RPBA.

IX. By letter dated 22 October 2014 the respondent announced that it would not attend the oral proceedings.

X. Oral proceedings before the board were held on 11 December 2014 in the absence of the respondent. During the oral proceedings the appellant withdrew its novelty objections and put forward arguments as regards lack of inventive step starting from document D1, which it now held to represent the closest prior art. At the end of the oral proceedings the chairwoman announced the board's decision.

XI. The appellant's arguments as submitted in writing and orally may be summarised as follows:

Main (sole) request

Inventive step (Article 56 EPC)

Document D1 represented the closest prior art. The subject-matter of claim 1 differed from the disclosure of document D1 only in the clonal character of the virus population. The technical effect of this difference was, according to paragraph [0079] of the opposed patent: "*to ensure or increase the genetic homogeneity of a particular virus strain and to remove defective interfering particles*". The objective technical problem was thus the provision of an improved virus-based therapy for the treatment of neoplasms in a mammal, where the improvement consisted in increased purity.

Defective virus particles could cause an unwanted stimulation of the patient's immune system. This was in particular disadvantegous in the treatment of cancer patients due to their usually weak constitution. A high genetic homogeneity of the administered virus particles was moreover desirable for safety reasons, as viruses with deviating sequences could show increased virulence and cause non-reproducible therapeutic effects. These aspects played a crucial role in market authorisation for viral preparations for therapeutic purposes. Hence, it was the constant aim of the person skilled in the field to improve virus-based therapies by reducing the number of defective particles in the virus preparation and by ensuring that the functional virus particles were genetically homogenous. The skilled person would thus be motivated to improve the purity and genetic

homogeneity of the virus population disclosed in document D1 and to provide a clonal virus population. Therefore, the skilled person would combine the teaching of document D1 with the virus purification methods disclosed in either document D4 or D11 and arrive at the claimed subject-matter in an obvious manner.

A comparison between a parent virus and a clonal population derived therefrom had not been carried out in the patent in suit. The technical effect - high therapeutic index of the clonal population - allegedly shown in document D14 could not be relied on for the formulation of the technical problem because this effect was neither disclosed in nor derivable from the patent in suit.

Document D12 would not have deterred the skilled person from using a clonal virus population in the treatment of neoplasms in mammals.

XII. The respondent's arguments as submitted in writing may be summarised as follows:

Main (sole) request

Inventive step (Article 56 EPC)

Document D1 represented the closest prior art. In the light of document D1, the objective technical problem was to provide an improved virus-based therapy for treating neoplasms. This problem was solved by the use of an interferon-sensitive clonal virus as defined in the claims of the main request.

Since the examples of the patent demonstrated a

credible anti-cancer activity for clonal viruses, the supplementary post-filed evidence provided by document D14 could be taken into consideration. This document, which compared clonal virus strain PV701 and the non-clonal parent strain MK701, showed that clonal viruses resulted in lower mortality of non-cancer cell types and a higher therapeutic index. The principal concept underlying the claimed invention was that clonal viruses demonstrated lower cytotoxicity to normal cells than non-clonal viruses.

Starting from document D1, the skilled person would have found no suggestion to use a clonal virus for the treatment of neoplasms. Even if in view of document D1 a skilled person could have produced a clonal virus, the question was whether he would have done so in the expectation of some improvement. Also, there was a general acceptance in the art that viral therapies should use non-clonal viruses, see for example document D12, page 1, last paragraph, which confirmed that NDV vaccines should use uncloned NDV. Hence, the skilled person seeking to prepare an improved anti-cancer therapy would have been led towards the use of a non-clonal virus.

XIII. The appellant requested that the decision under appeal be set aside and the patent be revoked.

The respondent had requested in writing by letter dated 10 December 2010 that the appeal be rejected in its entirety, i.e. that the patent be maintained as granted.

Reasons for the Decision

Procedural matters

1. The board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying only on its written case (Rule 115(2) EPC and Article 15(3) RPBA). The oral proceedings before the board took place in the absence of the respondent, who had been duly summoned but had decided not to attend.

2. The present decision is based on facts and evidence presented in the written procedure and on which the respondent has had an opportunity to comment.

Main (sole) request

Introduction

3. The patent in suit concerns the treatment of mammalian neoplasms with viruses that are able to cause the death of neoplastic cells which have a deficiency in the interferon-mediated anti-viral response while normal cells which possess an intact interferon-mediated anti-viral response limit the replication of the virus and are not killed. The viruses are RNA viruses, in particular paramyxoviruses such as Newcastle Disease Virus (NDV).

Inventive step (Article 56 EPC)

Closest prior art

4. The closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most

relevant technical features in common, i.e. requiring the minimum of structural modifications (see Case Law of the Boards of Appeal of the EPO, 7th edition 2013, section I.D.3.1).

5. It is common ground between the parties that document D1 represents the closest prior art with respect to the claimed subject-matter. Document D1 (see paragraph bridging pages 3 and 4; page 10, lines 11 to 15; examples) discloses a method of treating cancer in mammals by administering to the mammal an effective amount of a paramyxovirus. In a preferred embodiment the virus is NDV. The document discloses that NDV has direct cytolytic activity on the cancer cells and is capable of specifically differentiating cancer cells from normal, healthy cells. It is reported that one dose of NDV, given intralesionally to athymic mice, causes complete and permanent eradication of a wide variety of human tumours. Document D1 thus relates to the same purpose as the patent in suit - the treatment of cancer using interferon-sensitive, replication-competent RNA viruses capable of selectively killing neoplastic cells - and discloses one of the preferred viruses of the patent in suit, namely NDV.

The technical problem to be solved

6. There was no dispute among the parties that the subject-matter of claim 1 differed from the disclosure of document D1 only in the feature relating to the clonal character of the virus population.

7. Concerning the technical effect related to this difference, the board notes that paragraph [0079] of

the patent in suit discloses that "(i)*t is desirable to obtain a clonal virus to ensure or increase the genetic homogeneity of a particular virus strain and to remove defective interfering particles. Removal of defective interfering particles by cloning allows for increased purity in the final product as assessed by the number of total virus particles per infectious particle (e.g., the number of particles per PFU)*". Accordingly, the technical effect associated with the clonal character of the viruses which is disclosed in the patent in suit is the increase in genetic homogeneity of clonal versus non-clonal virus populations and the higher purity related to the removal of defective interfering particles.

8. The respondent, relying on post-filed document D14, which reports that in comparative experiments between the clonal virus strain PV701 and the non-clonal parent strain MK701 the clonal strain caused lower mortality in non-cancer cell types and a higher therapeutic index, argued that clonal viruses demonstrated lower toxicity to normal cells than non-clonal viruses.

9. The board notes that the patent in suit does not compare the efficacy of the parent non-clonal virus and a clonal population derived therefrom. Pursuant to paragraph [0074] of the patent in suit the viruses of the invention possess the following three characteristics: "*(i) they infect neoplastic cells resulting in their death; (ii) they are replication-competent in the neoplastic cells; and (iii) they are limited in killing of normal cells by the antiviral effects of interferon*". This passage refers to the specific cytotoxicity of the viruses of the invention towards neoplastic cells, but not to a possible advantage of cloned versus uncloned virus populations.

Indeed, the mention of "*limited killing of normal cells*" in this paragraph applies to any interferon-sensitive virus regardless of its clonality because, unlike neoplastic cells which are deficient in an interferon-mediated anti-viral response, normal healthy cells possess an intact interferon-mediated anti-viral response which protects them from virus-induced cytolysis, see paragraph [0050] of the patent in suit.

10. Accordingly, document D14 can not be relied on for the formulation of the technical problem because the technical effect shown in document D14 is neither disclosed in nor derivable from the patent in suit (see Case Law of the Boards of Appeal of the EPO, 7th edition 2013, section I.D.4.4.1).

11. It follows from points 7 to 10 above that starting from document D1 the problem to be solved is the provision of an improved virus-based therapy for the treatment of neoplasms in a mammal. The board is satisfied that the solution provided by the subject-matter of claim 1 solves this problem.

Obviousness

12. It remains to be answered whether or not the skilled person, when faced with the technical problem defined in point 11 above, would have modified the teaching in the closest prior art document D1 so as to arrive at the claimed invention in an obvious manner.

13. The prior art describes the provision of clonal sub-populations of NDV strains by plaque purification, see document D4, page 435, third full paragraph, and

document D11, page 116, lines 1 to 3.

14. Moreover, as submitted by the appellant, the skilled person would have known that the regulatory approval of any virus-based therapeutic composition would require detailed information indicating that the composition was safe and that the therapeutic effect was reproducible. For this it was necessary to provide a virus population which was devoid of defective particles which could cause an unwanted stimulation of the patient's immune system. A high genetic homogeneity of the administered virus particles was also desirable for safety reasons, as viruses with deviating sequences could show increased virulence and cause non-reproducible therapeutic effects. The respondent has not disputed this line of argument.

15. The respondent has however submitted that there was a general acceptance in the art that virus-based therapies should use non-clonal viruses, relying in this context on document D12 (page 165, last paragraph).

16. The board is not convinced that document D12 would have deterred the skilled person from using a clonal virus population in the treatment of neoplasms in mammals. The paragraph relied on by the respondent states that "[w]e *must be aware that the populations of Newcastle disease virus that spread in the field, or the populations that make up a vaccine stock* [note by the board: the NDV vaccine for use in chickens] *are not clonal*". In the board's view this corresponds to what was known in the art at the priority date, namely that "*both wild-type isolates and laboratory cultured strains of Newcastle disease virus contain several subpopulations*", see document D11, page 113, first

paragraph. A requirement that NDV should be uncloned when used in mammals, not in chickens, and for the treatment of neoplasms, and not as a vaccine, is not apparent from document D12.

17. Starting from the teaching of document D1 and faced with the problem of providing an improved virus-based therapy for the treatment of neoplasms in a mammal, the skilled person aware of the non-clonal character of NDV strains and of the regulatory requirements for obtaining marketing authorisation for viral preparations for therapeutic purposes would have readily considered providing a clonal virus population by plaque-purifying the NDV strain of document D1 pursuant to the teaching of document D4 or D11. He would thus have arrived at the subject-matter of claim 1 in an obvious manner.

18. Hence, the subject-matter of claim 1 and *a fortiori* the main (sole) request of which claim 1 forms a part fails to meet the requirements of Article 56 EPC. In the absence of an allowable request the patent is 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