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Datasheet for the decision of 28 February 2019

Case Number: T 1661/14 - 3.3.04

Application Number: 00928591.7

Publication Number: 1173484

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Language of the proceedings: EN

Title of invention:
Treatment of Fibrosis by Antagonism of IL-13 and IL-13 Receptor Chains

Patent Proprietor:
Genetics Institute, LLC
Government of the United States Of America, as represented by the Secretary, Department Of Health and Human Services

Opponents:
Schlich, George
Genentech, Inc.

Headword:
IL-13 antagonists for treating fibroma/GENETICS INSTITUTE

This datasheet is not part of the Decision.
It can be changed at any time and without notice.

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12(4)

Keyword:
Inventive step - all requests (no)

Decisions cited:

Catchword:

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Case Number: T 1661/14 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 28 February 2019

Appellant: (Patent Proprietor 1)	Genetics Institute, LLC 87 Cambridge Park Drive Cambridge, MA 02140 (US)
(Patent Proprietor 2)	Government of the United States of America, as represented by the Secretary, Department of Health and Human Services National Institutes of Health, Office of Technology Transfer, 6011 Executive Boulevard, Suite 325 Rockville, MD 20852-3804 (US)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 6 June 2014 revoking European patent No. 1173484 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chair G. Alt
A. Chakravarty
Members: J. Geschwind

Summary of Facts and Submissions

I. An appeal was filed by the patent proprietors (appellant) against the decision of the opposition division to revoke European patent No. 1 173 484. The patent is based on European patent application No. 00 928 591.7, with the title "*Treatment of Fibrosis by Antagonism of IL-13 and IL-13 Receptor Chains*".

II. Two oppositions were filed against the patent, opponents 1 and 2 are now respondents I and II to the appeal.

III. The appellant filed sets of claims of a main and seven auxiliary requests with the statement of grounds of appeal.

IV. Claims 1 and 2 of all claim requests read:

"1. Use of an IL-13 antagonist for the manufacture of a medicament for treating tissue fibrosis in a mammal, wherein said antagonist is selected from the group consisting of an IL 13bc protein, a soluble form of IL-13Rα1, an antibody to IL-13 or an IL-13 binding fragment thereof, an antibody to IL 13bc or an IL-13bc-binding fragment thereof, and an antibody to IL-13Rα1 or an IL-13Rα1-binding fragment thereof.

2. An IL-13 antagonist, wherein said antagonist is selected from the group consisting of an IL 13bc protein, a soluble form of IL-13Rα1, an antibody to IL-13 or an IL-13 binding fragment thereof, an antibody to IL 13bc or an IL-13bc-binding fragment thereof, and an antibody to IL-13Rα1 or an IL-13Rα1-binding fragment thereof for use in treating tissue fibrosis in a mammal".

These claims are identical to claims 1 and 2 as granted.

V. The following documents are mentioned in this decision:

D11: Chiaramonte M.G. et al., 1999, J. Immunol., Vol. 162, pages 920-930.

D13: Cheever A.W., 1997, MEM Inst. Oswaldo Cruz, Rio de Janeiro, Vol. 92, pages 689-692.

D15: Boros D.L., 1989, Clin. Microbiol. Rev., Vol. 2(3), pages 250-269.

D17: Wahl S.M. et al., 1997, Kidney Int., Vol. 51, pages 1370-1375.

D21: Wynn T.A. et al., 1995, Nature, Vol. 376, pages 594-596.

D24: Roux M. et al., 1994, J. Invest. Dermatol, Vol. 103, Abstract 288.

D39: Cheever A.W. et al., 1991, Infection and Immunity Vol. 59(11), pages 4071-4074.

D44: Olds R.G. et al., 1989, J. Immunol., Vol. 142(10), pages 3605-3611.

VI. The appellant's arguments relevant to the decision can be summarised as follows.

Main request

Inventive step (Article 56 EPC)

The opposition division concluded that document D11 represented the closest prior art for assessing the inventive step of the claimed invention (see point 3.69 of the decision under appeal). However, the opposition division erred in its assessment of the obviousness of the claimed subject matter vis-à-vis document D11.

The claims related to the medical use of an IL-13 antagonist for "*treating*" tissue fibrosis in a mammal. However, "*treating*" tissue fibrosis should not have been read to include "*preventing*" it. Although prevention had been the subject-matter of claim 11 as granted, this claim and its subject-matter were no longer present in the pending main request.

The patent made a distinction between "*treating*" and "*preventing*" (or "*inhibition formation of*") tissue fibrosis, as could be taken from paragraphs [0024] and [0025], or the last line on page 5 of the patent.

The opposition division stated in its decision that "*arguments that granuloma and fibrosis can be uncoupled would not appear to be supported by facts*" (see point 3.70 of the decision). However, the cited prior art clearly showed that granuloma and fibrosis were regulated independently, i.e. were two independent phenomena.

The documents D13, D24, D39 and D44 referred to in the decision under appeal did not "*merely relate to the observation that the degree of fibrosis does not always correlate with granuloma size*" but in fact showed that the reduction of granuloma size/volume or the reduction of granulomatous inflammation did not necessarily reduce fibrosis and *vice versa*.

For example, in document D39, both anti-IFNγ and anti-IL-5 treatment partially reduced granuloma volume, but did not have an effect on fibrosis following infection with Schistosoma eggs (see e.g. the abstract).

In document D44, mice infected with Schistosoma eggs were administered splenocytes or serum from uninfected or chronically infected mice. Transfer of serum reduced fibrosis but not granuloma size. The authors stated that "*[t]hese data indicate that a reduction in collagen content can occur in granulomas of infected animals without a reduction in granuloma size*" (page 3607, left column, end of 1st paragraph).

The authors of document D44 also noted that granulomatous inflammation modulated within 8 to 10 weeks of infection, but hepatic collagen content did not decrease until 3 to 4 weeks later, suggesting that "*these two events, granulomatous inflammation and fibrosis, might be under independent control*" (see e.g. page 3609, right column, end of upper paragraph).

Similarly, document D13 compared several literature reports in which granuloma size and fibrosis were dissociated and made the point that "*[w]e know nothing of the kinetics of collagen deposition in relation to granuloma size in humans*".

Accordingly, the cited prior art taught that reduction of granuloma size, as well as granulomatous inflammation, were not linked with the reduction of fibrosis.

Document D11 did not evaluate whether IL-13 antagonists were useful in treating fibrosis because the experiment described therein was stopped before fibrosis could even start to develop. Accordingly, in this document, the Schistosoma model was not used as a model for fibrosis. To determine whether IL-13 antagonists could be useful in treating fibrosis, further studies beyond those disclosed in document D11 would have been needed. These could have resembled those disclosed in document D21 in relation to IL-12.

The authors of document D11 saw "*no obvious difference in the amount of collagen deposition in or around the granulomas*" (page 926, right column, bottom of 2nd paragraph) in their model of Th2-driven inflammation and IgE production. Therefore, there was no reason for them (or another skilled person reading their paper) to use the model as a fibrosis model, since there was no expectation that collagen deposition would be affected by the administration of IL-13 antagonists.

In view of the above, it was not obvious from the cited prior art, in particular not from document D11, that IL-13 antagonists could be used in the treatment of fibrosis. The subject matter of the main request therefore involved an inventive step and complied with the requirements of Article 56 EPC.

VII. Respondent I made no substantive reply to the appellant's statement of grounds of appeal.

VIII. Respondent II's arguments relevant to the decision can be summarised as follows.

Admission of the main request and auxiliary requests 1 to 7 into the appeal proceedings - Article 12(4) RPBA

The main request and the seven auxiliary requests should not be admitted into the appeal proceedings. Their submission at this stage of the proceedings was unreasonable because the amendments they contained should have been made in response to the original opposition.

By deleting granted claims 11 to 25, including all dependent claims reciting "*inhibiting formation of tissue fibrosis*", the appellant was attempting to recast the meaning of the remaining claims by redefining the word "*treating*". The amendments led to the case in appeal being entirely different from that in the first instance. However, the case law of the Boards of Appeal was clear that the appeal proceedings could not be used to present a new case.

Main request

Inventive step (Article 56 EPC)

Regardless of the deletion of claims 11 to 25, the subject-matter of claims 1 and 2 encompassed both preventing and treating fibrosis. The opposition division was right to conclude that "*the solution provided in the claims cannot be considered inventive since it was apparently well known at the time of filing that 'the animal model for schistosoma is an art-recognised model for tissue fibrosis, not just for schistosoma-induced fibrosis' [....]. Therefore, [...]*

the skilled person, with a knowledge of D11 and the general technical field, would consider IL-13 antagonists, such as those described in [...] D11, for use as agents for the prevention of granuloma and the diseases resulting therefrom, including fibrosis"(see decision under appeal, point 3.69).

When given its ordinary meaning, "*treating*" fibrosis included "*preventing*" it. During the oral proceedings before the opposition division, the appellant had confirmed that fibrosis was always preceded by granulomatosis especially in the context of the schistosoma model. This was confirmed by documents in the art. For instance, document D11 disclosed that "*these findings are particularly important for schistosomiasis, since it is chronic egg associated pathology that leads to the development of severe disease in humans*" (see page 929, paragraph spanning left and right columns). In document D15 it was disclosed that "*Fibrosis enhances the disease pathology and contributes to the mortality of schistosomiasis mansoni. It follows the granulomatous inflammatory response*" (see page 257, left column, last paragraph, emphasis added, citations omitted).

Document D17 disclosed "*Schistosomiasis mansoni, a major cause of hepatic fibrosis in many developing countries, triggers a granulomatous inflammatory reaction in response to its eggs that lodge in the liver. The egg antigens are eliminated slowly, and the persistent granulomatous response leads to prolonged matrix synthesis and hepatic fibrosis*" (see page 1370, abstract and also page 1370, paragraph spanning left and right columns).

Accordingly, the opposition division was right to state "...*that granuloma and fibrosis can be uncoupled would not appear to be supported by facts: D13, D39, D42 and D44 merely relate to the observation that the degree of fibrosis does not always correlate with granuloma size - there is no evidence that fibrosis occurs without first the presence of granuloma*" (see decision under appeal, point 3.70).

This was significant because document D11 taught the skilled person that IL-13 antagonists abrogated granulomatous inflammation and its consequences (see decision under appeal, point 3.69). Therefore, the skilled person would have considered it obvious to also use IL-13 antagonists to abrogate the consequences of granulomatous inflammation, e.g. fibrosis (see decision under appeal, points 3.69 and 3.80).

IX. The board appointed oral proceedings for 7 February 2019 and subsequently issued a communication pursuant to Article 15(1) RPBA setting out its preliminary appreciation of some of the substantive and legal matters concerning the appeal (see point 10. of the Reasons, below).

X. With a letter dated 3 December 2018, the appellant withdrew their request for oral proceedings and indicated that they would not attend or be represented at the oral proceedings.

XI. With letters dated 7 December 2018 and 13 December 2018 respondents II and I, respectively, maintained their requests for oral proceedings only in case the board could not, in written proceedings, dismiss the appeal and maintain the decision of the opposition division to revoke the patent in its entirety.

XII. The board cancelled the oral proceedings.

XIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or alternatively on the basis of auxiliary requests 1 to 7, all filed with the statement of grounds of appeal.

XIV. Both respondents requested that the appellant's appeal be dismissed. Respondent II also requested that the main request and auxiliary requests 1 to 7 not be admitted into the proceedings.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Admission of the main request and auxiliary requests 1 to 7 into the appeal proceedings - Article 12(4) RPBA

2. Respondent II considered that the deletion of granted claims 11 to 25 led to a change of the subject-matter of the independent claims, thus leading to a situation where the appeal proceedings involved an examination of different subject-matter in comparison to that considered the opposition division. In view of this they requested all claim requests not be admitted into the oral proceedings.

3. However, all of the claim requests, filed with the statement of grounds of appeal, differ from those considered by the opposition division only in the deletion of dependent claims. The board takes the view that the deletion of dependent claims cannot and does not alter the subject-matter of the independent claims

because the deleted subject-matter remains encompassed by the unamended independent claims. Thus, the deletion of the dependent claims does not lead to a new factual or legal situation, i.e. the subject-matter of independent claims 1 and 2 remains the same. The board therefore sees no reason not to admit the above mentioned claim requests. The main request and auxiliary requests 1 to 7 are therefore in the appeal proceedings.

Main request and auxiliary requests 1 to 7

Claims 1 and 2

The claimed subject-matter

4. Claim 1, cast in the "Swiss-type" form, is for the second medical use of "an IL-13 antagonist" where the medical use or purpose is "treating tissue fibrosis in a mammal". The antagonist is selected from the group consisting of an IL-13bc protein, a soluble form of IL-13Rα1, an antibody to IL-13 or an IL-13 binding fragment thereof, an antibody to IL-13bc or an IL-13bc-binding fragment thereof, and an antibody to IL-13Rα1 or an IL-13Rα1-binding fragment thereof.

5. Claim 2 is the equivalent of claim 1 in the "purpose-limited" product format pursuant to Article 54(5) EPC.

Inventive step (Article 56 EPC)

The closest prior art

6. In the decision under appeal, the opposition division considered that document D11 represented the closest prior art for the claimed subject-matter. This has not

been disputed by the parties. The board therefore accepts document D11 as representing the closest prior art.

7. Document D11 discloses the use of an IL-13 antagonist (soluble IL-13Rα2-Fc fusion protein; sIL-13Rα2-Fc; "*which effectively blocks IL-13 binding to its receptor in vivo*"; see document D11, page 921, left-hand column, first paragraph) to significantly reduce the size of *Schistosoma mansoni* egg-induced primary pulmonary granuloma formation in unsensitized mice (see abstract). Document D11 further discloses that IL-13 is a mediator of granulomatous inflammation and tissue eosinophilia, and that blocking IL-13 with antagonists abrogates these effects (see page 927, left-hand column). The document also states that "*these findings are particularly important for schistosomiasis, since it is chronic egg-associated pathology that leads to the development of severe disease in infected humans*" (see page 929, paragraph bridging left and right-hand columns).

8. The difference between the disclosure in document D11 and the claimed subject-matter is the purpose of the treatment, i.e. the treatment of tissue fibrosis, as opposed to treatment of granuloma.

The problem and solution

9. In view of this difference, the board considers that the problem to be solved is the provision of a treatment for fibrosis. The board thus departs from the problem of "*provision of a new therapeutic use for IL-13 antagonists*", suggested in the decision under appeal. However, the difference in problem is largely

immaterial to the present decision, as will become apparent below.

Obviousness

10. In its communication pursuant to Article 15(1) RPBA, the board set out its preliminary view on inventive step and obviousness as follows: "*A key issue on inventive step appears to be the question of whether or not the skilled person, starting from the disclosure in document D11 representing the closest prior art, would have considered it obvious that an IL-13 antagonist could be used for "treating" fibrosis.*

*It appears to be common ground that the use of IL-13 antagonists for "*preventing*" granuloma formation and development was known (see document D11, abstract) and that, due to the causal link between granuloma formation and formation of fibrosis, the preventative treatment of fibroma using IL-13 antagonists was obvious.*

However, the parties do not agree on the answer to the question of whether or not "preventing" fibrosis formation inherently also involves "treating" fibrosis. The opposition division answered this question in the affirmative (see decision under appeal, point 3.70) and the board is currently inclined to agree with this assessment. The reason for this is that "treating" of fibrosis, as explained in the patent, is achieved through the inhibition of collagen formation (see Example 6). Thus it appears that therapy by IL-13 antagonism, be it termed "treatment" or "prevention" invariably involves inhibition of fibrosis via inhibition of collagen formation. There does not appear to be any disclosure in the patent of a "treatment"

using an IL-13 antagonist that would cause a reduction of an existing fibrosis".

11. In summary, the board considers that the skilled person, starting from document D11 representing the closest prior art and seeking to treat fibrosis, would have known from the same document that granuloma formation was a precursor to fibroma formation - "*chronic egg-associated pathology that leads to the development of severe disease in infected humans*" (see page 929, paragraph bridging left and right-hand columns). Thus, the skilled person would have considered that IL-13 antagonists could reasonably be expected to be able to treat (including prevent) fibroma, at least in patients suffering from schistosomiasis.

12. The board sees no reason to deviate from the preliminary view set out above, since the appellant made no substantive response to the board's communication and the board has no reasons of its own.

13. It follows that the subject-matter of claims 1 and 2 is considered obvious to the skilled person and does not meet the requirements of Article 56 EPC

14. In view of the foregoing, no claim request meets the requirements of the EPC. The appeal must be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

S. Lichtenvort G. Alt

Decision electronically authenticated