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Datasheet for the decision of 6 August 2020

Case Number: T 1958/16 - 3.3.04

Application Number: 01273862.1

Publication Number: 1379647

IPC: A61K38/17

Language of the proceedings: EN

Title of invention:
Antagonist antibodies of a mammalian cytokine or its receptor for the treatment of allergy

Patent Proprietor:
Merck Sharp & Dohme Corp.

Opponents:
Thirkettle, Linda Elke (opposition withdrawn)
Novartis AG
Dr. H. Ulrich Dörries

Headword:
IL-B50 antagonists for treating allergic diseases/MERK

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2)

Keyword:
Amendments - allowable (yes);
Sufficiency of disclosure - (yes);
Novelty - (yes);
Inventive step - (yes)

Decisions cited:
T 0609/02, T 1150/09

Catchword:

Europäisches Patentamt
European Patent Office
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Beschwerdekammern

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Case Number: T 1958/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 6 August 2020

Appellant: (Opponent 3)	Dr. H. Ulrich Dörries Fünf Höfe, Theatinerstr. 16 80333 München (DE)
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Party as of right: (Opponent 2)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Schlich, George Schlich 9 St Catherine's Road Littlehampton, West Sussex BN17 5HS (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on**

5 July 2016 concerning maintenance of the European Patent No. 1379647 in amended form.

Composition of the Board:

Chairman B. Claes
Members: D. Luis Alves
P. de Heij

Summary of Facts and Submissions

I. The appeal of opponent 3 (appellant) lies from the interlocutory decision of the opposition division that, account being taken of the amendments in the form of the main request, the patent and the invention to which it related met the requirements of the EPC. The patent is entitled "*Antagonist antibodies of a mammalian cytokine or its receptor for the treatment of allergy*" and was granted on European patent application No. 01 273 862.1, which was filed as an international application published as WO 2002/068646 ("application").

Independent claims 1 and 3 of the main request read:

"1. Use of an antagonist of IL-B50 (Figure 3A), which is a neutralizing antibody to IL-7Rα (SEQ ID NO: 2) or the Rδ2 (SEQ ID NO: 4) subunit or a complex comprising said subunits or an antibody which neutralizes IL-B50, for the manufacture of a medicament for the treatment of allergic diseases by blocking the function of human dendritic cells.

3. A pharmaceutical composition comprising an antagonist of IL-B50 (Figure 3A), which is a neutralizing antibody to IL-7Rα (SEQ ID NO: 2) or the Rδ2 (SEQ ID NO: 4) subunit or a complex comprising said subunits or an antibody which neutralizes IL-B50, for use in the treatment of allergic diseases by blocking the function of human dendritic cells."

II. Opponent 1 also filed an appeal against the decision but subsequently withdrew their opposition.

III. Three oppositions were filed. The patent had been opposed as a whole under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and on the grounds under Article 100(b) EPC and Article 100(c) EPC.

IV. In their statement setting out the grounds of appeal, the appellant contested the decision of the opposition division. Further submissions were filed with a subsequent letter.

V. With their reply to the statement of grounds of appeal, the patent proprietor (respondent) filed auxiliary claim requests 1 to 3.

VI. The board summoned the parties to oral proceedings and, in a communication pursuant to Article 15(1) RPBA, informed them of the preliminary opinion of the board on some of the issues in the appeal.

VII. By letter dated 9 March 2020, the respondent filed further submissions and auxiliary claim requests 1 to 11 to replace the auxiliary requests filed earlier.

The only two claims of auxiliary request 4 were identical to claims 1 and 3 of the main request subject to the decision under appeal (see section I.).

VIII. The appellant and opponent 2, a party as of right, were not represented at the oral proceedings, as announced by telephone conversation of 30 July 2020 and by letter dated 12 June 2020, respectively.

At the oral proceedings, the respondent made auxiliary request 4 its main request. A further document was

filed containing a list of passages of the patent application.

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

IX. The following documents are cited in this decision:

D1: WO 01/012672

D2: WO 00/017362

D5: Stirling, R.G. and Chung, K.F., British Medical Bulletin 56(4), 2000, pages 1037-1053

D20: Soumelis *et al.*, Nature Immunology 3(7), 2002, pages 673-680

D23: Immunobiology, 4th edition (1999), pages 461-467 and 477-478

D28: Chu, D.K. *et al.*, J. Allergy Clin. Immunol. 131, 2013, pages 187-200

D29: Wynn, T.A., Nat. Rev. 15, 2015, pages 271-282

D30: Borthwick, L.A. *et al.*, Mucosal Immunol., 2016, pages 38-55

D33: Blazquez, A.B. *et al.*, Gastroenterology 139, 2010, pages 1301-1309

D34: Gauvreau, G.M. *et al.*, N. Engl. J. Med. 370, 2014, pages 2102-2110

D35: Watson, B. and Gauvreau, G.M., Expert Opin. Ther. Targets 18(7), 2014, pages 771-785

D36: Abbas *et al.*, Nature 383, 1996, pages 787-793

X. The appellant's arguments submitted in writing relevant to this decision may be summarised as follows.

Main request

Amendments - Article 123(2) EPC

The claimed combination of the features "allergic diseases", "neutralizing antibody" and "human" in claims 1 and 2 had no basis in the application as filed. When relying on page 14, lines 8 to 16, which disclosed the use of antagonists for treating allergic disorders, to arrive at the subject-matter of the claims, it would have been necessary to select other passages of the application disclosing that the antagonist was an antibody, that the antibody could be directed to the receptor or each of its subunits, that the antibody was a neutralising antibody and that the dendritic cells were human dendritic cells. None of these features was emphasised in the application as filed. Thus, combining these was arbitrary and contradicted the requirements of Article 123(2) EPC.

Additionally, the specific sequences defined by the SEQ ID NOs in the claims also constituted a selection.

Sufficiency of disclosure - Article 83 EPC

The antibodies as defined in the claims were not sufficiently disclosed in the patent for two reasons. One, the patent referred to an IL-B50 sequence

containing the signal peptide (Figure 3A) instead of referring to the mature sequence of IL-B50. Two, while the claims referred to neutralising antibodies, the patent did not provide a single example of an antibody inhibiting the binding of IL-B50 to its receptor.

The patent did not disclose the suitability of the neutralising antibodies referred to in the claims for treating allergies because (i) no experiments were carried out with antibodies or other antagonists, (ii) the patent did not use an *in vivo* model and (iii) the patent, in its evaluation of the experimental results, instead of concluding on the usefulness of IL-B50 antagonists for treating allergic diseases, pointed to other conditions (paragraphs [0215] and [0216]). Post-published disclosures could not be taken into account for assessing sufficiency of disclosure because this could only be allowed to back up findings in the patent.

The patent did not show the suitability of IL-B50 antagonist antibodies for all the embodiments encompassed by the claims, which referred generically to allergic diseases.

The patent did not provide information on which allergic diseases the IL-B50 antagonists could be useful for. Thus, identifying the diseases that could be treated would have been an undue burden for the skilled person.

Specifically, there were contradictions between the data shown in Figure 4E of the patent and the disclosure in post-published documents D20/D21 and D28. On the one hand, Figure 4E showed IL-B50 expression in various tissues and revealed the absence of its

expression in skin. The skilled person would thus not have derived that IL-B50 antagonists were suitable for treating skin allergies. Nevertheless, this was the case as disclosed in document D20 for atopic dermatitis (page 678, left-hand column, paragraph bridging pages 678 and 679 and Figure 8).

On the other hand, Figure 4E of the patent showed IL-B50 expression in intestine. However, document D28 disclosed that targeting IL-B50 had no effect on peanut allergy (page 188, left-hand column, first full paragraph and paragraphs bridging the columns on this page, and Figure E2, panels B and C). It further showed that an antibody to IL-B50 did not have any effect on house dust mite (HDM)-induced allergic asthma (page 188, right-hand column, Figure E1, panels B and C).

These facts thus substantiated serious doubts that IL-B50 antagonists were suitable for treating particular allergic diseases. The disclosure in document D34 did not allow concluding that IL-B50 was involved in HDM allergy.

The feature "*by blocking the function of human dendritic cells*" did not limit the claimed subject-matter because it merely defined a mechanism of action inherent to IL-B50 antagonists and because it was meaningless in so far as it did not define which function was to be blocked. Thus, it did not exclude from the claimed subject-matter allergic diseases not involving dendritic cells. This feature did not exclude food allergy as discussed in document D28. This document disclosed that peanut mimicked IL-B50 in its interaction with dendritic cells and that IL-B50 was redundant in the mechanism of Th2 induction in peanut

allergy (page 190, paragraph bridging the two columns). Nonetheless, dendritic cells were involved in this mechanism.

Document D33 disclosed allergies with IL-B50 involvement independent of dendritic cells (abstract). If the feature "*by blocking the function of human dendritic cells*" was seen as limiting the claimed subject-matter, the disclosure in this document substantiated doubts that every allergic disease could be treated by blocking the function of dendritic cells.

The disclosures in documents D29 and D30 called into question that Th2-mediated immune responses could be suppressed by blocking dendritic cells via an IL-B50 antagonist for every allergic disease. Document D29 disclosed that dendritic cells did not seem to be crucial in the maintenance of Th2-dependent immune responses and might be involved merely in their initiation. This was confirmed in document D30, which disclosed that macrophages, and not dendritic cells, were critical in the maintenance of IL-13-dependent lung inflammation. Thus, IL-B50 antagonists were not suitable for treating allergic diseases via the blocking of dendritic cell function.

There were striking parallels between the case at issue and the case underlying decision T 1150/09. Therefore, the same conclusion should be reached. The opposition division held that the case at hand differed from that underlying decision T 1150/09 because of the lower complexity of allergic diseases as compared to cancer. However, no evidence had been presented in this respect.

Novelty - Article 54 EPC

Document D1 disclosed the CRCGCL receptor, designated as the IL-B50 receptor subunit Rδ2 in the patent (see page 3, second paragraph and SEQ ID NO: 2). Antagonist antibodies to this receptor were disclosed as useful for treating allergic diseases such as asthma and allergic encephalomyelitis (see page 7, first full paragraph and paragraph bridging pages 8 to 9 as well as page 155, lines 19 to 20). The functional feature "*by blocking the function of human dendritic cells*" in the claims was inherent to an antibody to the IL-B50 receptor. Thus, document D1 disclosed the claimed subject-matter.

The same requirements applied to sufficiency of disclosure of documents of the prior art and sufficiency of disclosure of the patent (see decision T 1437/07). Document D1, like the patent, disclosed that agonists of the receptor could be used to skew the immune response towards a Th2 response (see page 148, lines 23 to 24). The disclosure in document D23 that blocking development of a Th2 response was a strategy in the treatment of allergic diseases applied equally when assessing sufficiency of disclosure in document D1 and in the patent. Thus, the disclosure in document D1 of receptor antibodies for treating allergy was enabling.

Inventive step - Article 56 EPC

The problem of providing a treatment for allergic diseases was not solved by the claimed subject-matter. The disclosure in document D28 substantiated doubts in this respect. The patent provided nothing beyond an in *vitro* assay without plausibly showing that treatment

success in allergic diseases across the scope of the claims could be expected.

The claimed subject-matter did not involve an inventive step with regard to the disclosure in each of documents D2 and D5.

Document D2 disclosed therapies for immune disorders (page 13 to 14, last paragraph and page 39) and thus addressed a similar technical problem as the claimed invention. It also had the most relevant features in common with the claimed subject-matter because it related to IL-B50 and antibodies to it as well as their medical uses (see page 7 and claims 19 and 20). The only difference between the claimed subject-matter and the disclosure in document D2 was that it specified allergic diseases within the general group of immune disorders.

The claimed subject-matter related to allergic diseases instead of immune disorders in general. The objective technical problem was thus to provide IL-B50 antibodies for use in an alternative immune disorder. Document D2 disclosed on page 3, lines 1 and 2, that mast cells played a role in allergy-related disorders. On page 2, it was mentioned that B cells and T cells were important in immune responses. Document D2 thus would have provided an incentive to treat allergic diseases as claimed.

The claimed subject-matter would also have been obvious to the skilled person when starting from the disclosure in document D5 representing the closest prior art in view of the disclosure in document D1.

The skilled person would have known that blocking the development of a Th2 response was a strategy in the treatment of allergic diseases. In view of the disclosure in document D1 of a link between IL-B50 and Th2 responses (see page 148, lines 23 to 24), the skilled person would have had an incentive to provide an antagonist of the IL-B50/TSLP receptor for use in treating allergic diseases.

XI. The respondent's arguments submitted during the oral proceedings and in writing relevant to this decision may be summarised as follows.

Main request

Amendments - Article 123(2) EPC

The requirement for direct and unambiguous disclosure did not require literal support in the application. It would have been sufficient for the skilled person that the technical content claimed was disclosed in the application as filed.

The application taught that the receptor for IL-B50 consisted of the two subunits IL-7Rα and Rδ2, that it was expressed in dendritic cells, that dendritic cells were activated in presence of IL-B50 and that such activated dendritic cells induced naive T cells to the Th2 phenotype. It also taught that interfering with this receptor-ligand binding could be used for therapy. The passage disclosing the treatment of diseases with antagonists, including allergic diseases, was immediately followed by the reference to the interaction between IL-B50 and its receptor (see page 14). Thus, the skilled person would have been taught that the antagonists should interfere with this

interaction. Antibodies were the antagonists particularly addressed in the application (see page 3, line 23; page 4, lines 17 to 21; page 14, lines 10 to 15; page 39, lines 5 to 11 and page 49, line 22) and were identified as binding to the receptor complex or its subunits or to IL-B50 (see page 3, last paragraph and page 4, first paragraph). Such antibodies should be neutralising antibodies (see page 3, line 23; page 4, line 4 and page 39, lines 5 to 11) which blocked the function of the dendritic cells (see page 14, line 14).

The application as a whole focused on humans, referring to the human receptor, human IL-B50 and human dendritic cells and disclosing the sequences of human IL-B50 and human IL-B50 receptor subunits (see page 3, lines 12 and 13; page 5, lines 11 to 16 and 21 to 23; page 13, lines 15 to 20; Figure 3A; SEQ ID NOs 2 and 4; page 57, lines 12 to 16; and page 59, lines 10 to 29).

Thus, the claims would not have presented the skilled person with new information.

Sufficiency of disclosure - Article 83 EPC

The patent disclosed the suitability of antibodies to IL-B50 for achieving the claimed therapeutic effect (see paragraphs [0196], [0199] and [0212]). The patent taught (i) that IL-B50 activated dendritic cells, (ii) that these dendritic cells primed naive T cells to become T helper cells and (iii) that these T helper cells produced Th2 cytokines. Documents D23 and D36 represented the common general knowledge and linked Th2 responses to allergic diseases (see document D23, page 467, paragraph 2 and figure on page 477 and document D36, page 792, left-hand column, last paragraph).

The preparation of antibodies to a given protein was routine work and the patent disclosed in paragraph [0212] tests on binding between Il-B50 and its receptor and associated measurable biological activities. The patent taught that the antibodies should bind to IL-B50 or its receptor, inhibiting their interaction (see paragraphs [0016], [0133] and [0160]).

Document D28 was not conclusive on the suitability of antibodies to IL-B50 for treating allergies as an effect on allergic diseases was not denied (see page 188, last sentence) and it was instead stated that the peanut and HDM allergens might be mimicking the IL-B50 effect on dendritic cells. Moreover, the experiments in this document were based on mice and therefore on a different biology to human IL-B50 (TLSP) (see document D20, page 673, sentence bridging the two columns). Additionally, document D34 disclosed that in asthma patients exposed to HDM, there was an improvement in the allergic reaction with the administration of an IL-B50 antibody (see page 8, left-hand column, first paragraph and Table S2). Thus, the results reported in document D34 were more relevant to the question of the suitability of an antibody to IL-B50 for the treatment of an allergy than those obtained in document D28 on the basis of an animal model. Additionally, document D35 presented a review on studies showing the usefulness of antibodies to IL-B50 or its receptor in the treatment of asthma, including HDM-induced asthma (see page 780, Table 2).

Figure 4E and paragraph [0195] of the patent did not state whether the reported IL-B50 expression in skin tissue related to healthy or diseased tissue, and it should therefore be assumed it concerned healthy

tissue. In any case, it could not be said that the patent disclosed an absence of IL-B50 expression in diseased skin tissue. Thus, there was no contradiction with the disclosure in document D20.

The possibility of the existence of additional mechanisms of inducing a Th2 response, independent of the activation of dendritic cells (see document D33), did not prove that the blocking of dendritic cell function by IL-B50 antibodies did not have an effect on allergy.

Document D29, in Figure 2, supported the findings in the patent that IL-B50 induced dendritic cells, which in turn induced T cells to produce pro-inflammatory cytokines. Even if there were additional mechanisms involved in the triggering or maintenance of allergic diseases, this did not disprove the mechanism disclosed in the patent. This document additionally disclosed that IL-B50 antibodies could be used to treat allergy (see page 279, left-hand column, lines 35 to 39). This was also confirmed in document D35 (see page 778, right-hand column, first paragraph). Also, document D30 did not show that IL-B50 was not involved in the maintenance of allergy.

The skilled person would have been able to establish for which allergic diseases the antibody provided a suitable treatment by looking for activity of IL-B50. It could not be required that the patent provide data for each allergic disease.

Novelty - Article 54 EPC

Document D1 mentioned both the IL-B50 receptor subunit Rδ2 and antibodies to it as being useful for treating a

number of diseases (see "Summary of the invention" on page 7, third paragraph). The list of diseases that could be treated with an antagonistic antibody to the receptor included immunodeficiencies (see page 7) and autoimmune diseases (see pages 8 and 9); viral, bacterial or fungal infections (see pages 143 to 145); immunological disorders (see page 146 and following); diseases associated with mucous membranes of the body (see page 150 and following); immune-system related disorders; fibroses; cancer; and AIDS (see page 157). This long list showed that it was not known in which diseases the receptor was indeed involved. Moreover, for all these diseases, both antagonist and agonist antibodies were presented as useful. Thus, for a given disease, there was no teaching on whether the receptor activity ought to be enhanced or suppressed. The passages on pages 155 and 148, mentioning allergy and the bias towards a Th2 response, respectively, were selected from the disclosure in document D1, which, however, covered many more medical uses of the agonists and antagonists. Nevertheless, document D1 did not disclose specific properties of the receptor which made plausible any specific therapeutic application.

Inventive step - Article 56 EPC

Document D5 disclosed the treatment of asthma and atopic dermatitis, both being allergic diseases. On the other hand, document D2 disclosed IL-B50 antibodies but did not address the treatment of allergic diseases. The appellant had not made a convincing argument why the disclosure in document D2 rather than in document D5 represented the closest prior art.

Document D5 was silent on targeting the interaction between IL-B50 and its receptor as a therapy for

allergy. The objective technical problem was thus the provision of an alternative target for treating allergic diseases.

The skilled person would not have derived from document D1 that IL-B50 provoked a Th2 response because document D1 did not disclose that IL-B50 activated dendritic cells which primed T cells to induce a Th2 response. The mention of Th2 responses on page 148 of this document had to be read in the context of the document as a whole, which did not disclose how the IL-B50 receptor was involved in any specific disease much less in allergic diseases (for the same reasons as presented above with regard to novelty).

The claims were limited by the expression "*by blocking the function of human dendritic cells*".

The prior art did not disclose an effect of IL-B50 on dendritic cells and, even assuming it had, the skilled person would have expected that IL-B50 was involved in Th1 mediated immune responses. Also, document D2 would not have motivated the skilled person to select IL-B50 as a target for treating allergies because it highlighted the similarity between IL-B50 and IL-7, and the latter was known as a T-cell and B-cell growth factor and not as a cytokine involved in allergy (see document D19). Thus, the skilled person starting from the disclosure in document D5 would not have targeted IL-B50 to treat allergic diseases, much less by blocking dendritic cell function.

Document D2 provided speculations on possible functions of IL-B50 without mentioning allergic diseases (see page 9, first paragraph and page 13, last paragraph to page 14, first paragraph). The IL-B50 receptor was not

identified, and expression data was the only experimental data disclosed.

Considering the objective technical problem to be the provision of alternative uses of IL-B50 (TSLP), the identification of IL-B50 as a target for treating allergic diseases would not have been obvious from document D2. That would have required working against what was conveyed in this document which taught away from a role for IL-B50 in Th2 responses (see page 55, last paragraph). It would not have been possible to assay for the IL-B50 function because the receptor had not been identified. Furthermore, the prior art rather associated dendritic cells with Th1 responses (see documents D17 to D19).

Thus, it would not have been obvious to the skilled person to provide IL-B50 antagonists for treating allergic diseases.

XII. Opponent 2 has not filed substantive submissions in these appeal proceedings.

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

The respondent requested that the patent be maintained on the basis of the claims according to the main request, filed during the oral proceedings of 6 August 2020.

Reasons for the Decision

Admissibility of the appeal

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

Parties not represented at oral proceedings

2. The appellant and opponent 2, a party as of right, were not represented during the oral proceedings as announced previously. In accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020, the oral proceedings were held in the absence of these parties, which were considered as relying on their written case.

Main request

Amendments - Article 123(2) EPC

3. The appellant submitted that the combination of the features "allergic diseases" and "neutralizing antibody" as well as the feature "human" had no basis in the application as filed.

4. It is established case law of the boards of appeal of the European Patent Office that literal support for amendments in a patent is not required under Article 123(2) EPC in so far as the amended or added features reflect the technical information that the skilled person, reading the application as filed, would have derived from its content considered in its entirety. What is required is that amendments are made only within the limits of what the skilled person would have derived directly and unambiguously, using common

general knowledge, and seen objectively and relative to the date of filing, from the whole of the application as filed (see decisions cited in Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, II.E.1.3.1 and 1.3.2).

5. The application as filed discloses that the receptor complex for IL-B50 consists of the IL-7Rα and Rδ2 subunits (page 3, first and second paragraphs, in particular lines 14 to 15, and page 8, third paragraph) and that this allows studying mechanisms involving IL-B50 (page 3, first paragraph and paragraph bridging pages 8 and 9); that both receptor subunits are expressed in dendritic cells (page 62, second paragraph); that IL-B50 agonists or antagonists (the latter being either neutralising antibodies to IL-B50 or antibodies to the receptor complex or either of its subunits) can be used to modulate the physiology or development of cells expressing the receptor (page 3, last paragraph); that neutralising antibodies to each of the receptor subunits or their complex (antagonists) may be used to inhibit IL-B50-dependent cell signalling (page 4, first paragraph); and that IL-B50 has an activating effect on dendritic cells (page 13, third paragraph).

6. Subsequently, the application discloses applications of modulating IL-B50 mediated signalling: "*Dendritic cells are also involved in autoimmune diseases, allergic diseases, graft-versus-host disease and rejection of solid organ transplants. Therefore, enhancing dendritic cell function allows for treatment of tumors and infectious diseases. Similarly, blocking dendritic cell function provides therapies for autoimmune diseases, allergic diseases, graft-versus-host diseases and transplantation associated rejection.*

Thus, IL-B50 may be used in enhancing dendritic cell function in treating cancers and infectious diseases and IL-B50 antagonists may be used in blocking the function of dendritic cells in treating autoimmune diseases, allergic diseases, graft-versus-host diseases and transplantation associated rejection. The elucidation of the IL-B50 receptor subunits, therefore, allows for the identification of agonists and antagonists of IL-B50 for use in treating the aforementioned diseases." (see page 14, lines 8 to 18).

7. Thus, the above passage teaches that IL-B50 antagonists are useful for treating allergic diseases by blocking the function of dendritic cells and that such antagonists may be identified using the disclosed IL-B50 receptor. The passage discloses that the antagonist is used for treating a disease and therefore as a medicament. The single selection of allergic diseases from the diseases mentioned in this passage does not constitute an extension beyond the content of the application as filed.

8. The application emphasises throughout that embodiments of the antagonists are antibodies that interfere with the interaction between IL-B50 and its receptor complex or either of its subunits (see e.g. page 3, lines 23 and 24; page 4, lines 4 and 5; page 4, lines 17 to 21; page 39, line 5 and page 49, lines 22 to 23). The only alternative antagonist mentioned is a mutein of IL-B50, which is, however, not discussed further. The skilled person would therefore have taken from the application as a whole the above-mentioned antibodies are the preferred antagonists.

9. In this context, the skilled person would have read "neutralizing antibody" or "antibody which neutralizes" as for example used in the passages on page 4, lines 3 to 5 and page 3, line 23 as generally referring to such antagonising antibodies. This reading is confirmed by the distinction made in the application between antibodies for therapeutic and those for diagnostic use; the former being antagonist antibodies, and the latter being non-neutralising antibodies (see page 39, second paragraph).

10. Thus, in the board's view, defining in the claims the antagonists as neutralising antibodies, directed either to the cytokine or its receptor or receptor subunits, would not have presented the skilled person with technical information not disclosed in the application as filed.

11. As concerns the feature "human dendritic cells", the application discloses the human receptor for human IL-B50 (see page 5, lines 11 to 16, which refer to Figure 3A and SEQ ID NOs 2 and 4; and page 57, lines 12 and 13). The examples disclose experiments describing the effect of cytokine-receptor interaction on human dendritic cells (see page 5, lines 21 to 23; and page 59, lines 20 and 29). For the skilled person reading the application, this context would have applied also to the treatment of allergic diseases as disclosed on page 14, even if that passage does not explicitly mention "human" when referring to dendritic cells. In light of the above, the board concludes that the skilled person would not have been presented with new technical information when reading in the claims that the targeted dendritic cells are human.

12. It furthermore follows that the reference in the claims to the amino acid sequences depicted in Figure 3A and SEQ ID NOs 2 and 4, as corresponding to IL-B50, and receptor subunits IL-7Rα and Rδ2, respectively, would not have presented the skilled person with new technical information either since these are the amino acid sequences disclosed in the application for the human proteins.

13. Consequently, the claimed subject-matter does not extend beyond the content of the application as filed (Article 123(2) EPC).

Sufficiency of disclosure - Article 83 EPC

14. Experimental data in the patent demonstrate that dendritic cells express both subunits of the receptor complex for IL-B50, i.e. IL-7Rα and Rδ2, and that the interaction of IL-B50 with dendritic cells results in their activation (see paragraphs [0204] and [0206] and Figures 4A and 4C [Note: the human receptor subunit R2δ is also designated as hTSLPR in the patent]). It is further demonstrated that activated dendritic cells induce the production of IL-4, IL-13 and TNF-α in naive T cells (see paragraphs [0041] and [0212]), a cytokine profile indicative of the importance of IL-B50 for Th2 effector functions relevant in the context of infections and allergic and autoimmune diseases (see paragraph [0159]).

15. Indeed, it was common general knowledge that a Th2 response was involved in the development of allergy and that strategies for the treatment of allergies targeted the Th2 response and aimed to alter the Th2/Th1 balance

(see document D23, page 467, second paragraph and figure on page 477).

16. In view of the considerations above, the board is convinced that the application, read with the common general knowledge, would have disclosed to the skilled person the suitability of antibodies interfering with the interaction of IL-B50 with its receptor for the treatment of allergic diseases.

17. The appellant argued that the application lacked any experimental results obtained *in vivo*. However, according to the case law of the boards of appeal of the EPO, to meet the requirements of sufficiency of disclosure, it is not required that results of the administration of the claimed compositions obtained in clinical trials or in experiments in animal models be disclosed (see decision T 609/02 and further decisions cited in Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, II.C.7.2).

18. To fulfil the requirements of sufficiency of disclosure, it is likewise not required that in the patent the experimental section directly link the claimed therapeutic application to the mechanism it relies on, in the case at hand, the effect of IL-B50 on dendritic cells and induction of a Th2 phenotype. Relevant for the purposes of sufficiency of disclosure is whether the disclosure in the patent or the common general knowledge would have enabled the skilled person to obtain the compound to be applied and to apply it and if it is demonstrated that the intended therapeutic effect can be achieved (*ibid.*, page 374). Therefore, no merit can be seen in the appellant's argument that in the patent the experimental section is not immediately followed by a conclusion on the specific suitability of

IL-B50 antagonists to the treatment of allergic diseases. In fact, in which part of the patent the information is conveyed plays no role.

19. Since the patent has to be read from the standpoint of the skilled person, the board cannot find persuasive the appellant's argument that the skilled person would not have been able to put the invention into practice because the amino acid sequence of IL-B50 given in Figure 3A includes the signal peptide. This would have posed no difficulties to the skilled person, who would have known that the antibodies should be raised to the protein not including the signal peptide. Likewise, the board does not find convincing the argument based on the lack of examples of antibodies according to the claim in the patent. The patent states at multiple instances that neutralising antibodies should interfere with the binding of IL-B50 to its receptor (see paragraphs [0133] and [0134]). The board is thus convinced that the patent teaches how to provide antibodies suitable for the treatment of allergies. Questioning the meaning of "neutralizing antibodies" in the claim is not sufficient to establish that antibodies according to the patent, i.e. antibodies binding to IL-B50 or its receptor and interfering with the binding between the two, cannot be provided.

20. The appellant, in a further line of argument, submitted that the patent did not show the suitability of IL-B50 antagonists for the treatment of all allergic diseases as claimed and would not have provided the skilled person with sufficient information to differentiate allergic diseases which could be treated with IL-B50 antagonists from those which could not. To the contrary, it argued, what the skilled person would have inferred from the IL-B50 tissue expression shown in the

patent (Figure 4E) would have been in contradiction with the disclosure in post-published documents D20 and D28. From a lack of IL-B50 expression in skin, as shown in the patent, the skilled person would not have expected a therapeutic effect of IL-B50 antagonists on skin allergies. Nevertheless, document D20 disclosed increased expression of IL-B50 in skin lesions of patients with atopic dermatitis [Note: in this and several other documents in the proceedings, IL-B50 is designated as TSLP]. The patent showed IL-B50 expression in intestine, but document D28 disclosed a lack of efficacy when targeting IL-B50 for treating peanut allergy.

21. The board notes that the application does not disclose lack of IL-B50 expression in patients suffering from atopic dermatitis since it does not indicate the source of the analysed skin tissue, which must be assumed to be healthy skin. There is therefore, in the board's view, no contradiction between the IL-B50 tissue expression shown in the patent and the disclosure in document D20.

22. In the board's view, the disclosure in document D28 likewise does not amount to serious doubts that allergic diseases can be treated by IL-B50 antagonists.

23. The appellant argued that document D28 showed that antibodies to IL-B50 were not suitable for treating peanut and house dust mite (HDM) allergies, which both fall within the allergic diseases in the claims, thus establishing serious doubts on the suitability of such antibodies for the treatment of all allergies. The appellant pointed to results in this document showing no improvement with IL-B50 antibody in a HDM and in a peanut allergy mouse model.

23.1 Document D28 aims at investigating the contribution of IL-B50 (TSLP), IL-25 and IL-33 in the development of allergy to peanut and HDM. It concludes that IL-33, rather than IL-B50, plays a role in initiating Th2 responses to these allergens and that "*multiple molecular pathways can initiate T_H2 immunity*" (see abstract). It suggests that the allergens used were mimicking IL-B50 (see page 190, right-hand column, last sentence of first and second paragraphs). It also states that "*In stark contrast to the increasingly prevalent opinion that TSLP is a master regulator of T_H2 responses and thus atopic disease, we found that TSLP was dispensable for the generation of IL-4-dependent humoral and cellular immunity to HDM or peanut.*" (see page 188, left-hand column, second paragraph); "*These data, generated by using the common aeroallergen HDM, are in sharp contrast to the results published by 2 different groups reporting TSLP-dependent lung T_H2 responses to the surrogate allergen OVA in mouse models involving intraperitoneal alum-driven sensitization protocols. (...) Thus although our data confirm a role for TSLP in this OVA model, they do not support the contention that TSLP is pervasively a key factor in the initiation of allergic asthma.*" (see page 188, right-hand column, last paragraph, emphasis by the board).

23.2 The above passages thus do not contradict the general mechanism disclosed in the patent involving IL-B50 in the activation of dendritic cells and the induction of a Th2 response. Moreover, the authors note in several instances that their results are "*in stark contrast to the increasingly prevalent opinion*" and "*in sharp contrast to the results published by 2 different groups*" (quoted from the previous paragraph).

Accordingly, the board is not convinced that the doubts raised in this document amount to serious doubts as required to question the sufficiency of the disclosure in the patent, whether in the context of allergy to peanut or HDM.

23.3 Other documents in the appeal procedure, specifically documents D34 and D35, further substantiate this assessment of the disclosure in document D28. Documents D34 and D35 refer to results of a clinical trial and an animal model, respectively, that show an effect of an IL-B50 antibody on allergen-induced asthmatic response, the allergen including the HDM allergen (see document D34, title, abstract, conclusions and Table S2 (in the Supplementary Appendix); and document D35, Table 2). This is in contradiction with the results reported in document D28 for the same allergen. Although the appellant has contested that any conclusion may be drawn from the results in document D34 because of the small number of patients in the experiments, the board notes that these results concern patients whereas those in document D28 are based on modelling of the allergy. In view of this, the board does not see a reason to discard the results in document D34 in favour of those in document D28.

24. Taking the disclosure in documents D28, D34 and D35 into account, the board comes to the view that the questioning in document D28 of a role for IL-B50 in peanut and HDM allergies is not conclusive so as to constitute serious doubts that IL-B50 is a suitable target for treating peanut and HDM allergies. Therefore, the board cannot conclude from this disclosure that targeting IL-B50 is not suitable for treating allergy to peanut or HDM.

25. The appellant referred to decision T 1150/09 which dealt with claims directed to the therapeutic application of placental growth factor (PIGF) in the treatment of cancer. In this decision, the board held that the patent did not provide sufficient information for the skilled person, taking into account their common general knowledge, to know which cancers could be treated according to the invention. The board arrived at that conclusion based on evidence that PIGF was not involved in all types of cancer, together with the absence in the patent of a disclosure of criteria for the skilled person to identify which cancers could be treated out of a generic list.

26. However, the board considers the case at hand to differ from that underlying decision T 1150/09 in at least the crucial point that in the current case the board is not convinced that there are allergic diseases in which IL-B50 plays no role and for which IL-B50 antagonists have been demonstrated to be an unsuitable treatment.

27. The appellant referred to documents D29 and D30 to question the link between IL-B50, dendritic cell activation and Th2 responses. The board holds the appellant's argument based on the disclosure in documents D29 and D30 that dendritic cells are not crucial in the maintenance of every Th2 immune response and are possibly involved only in their initiation not to be persuasive. These documents do not deny a role for IL-B50 and dendritic cells in inducing a Th2 response, and neither has this been argued by the appellant. The board concludes therefore that whereas for some allergic diseases or some stages of these diseases IL-B50 and dendritic cells might not play a central role, it is not questioned that they do play some role. Therefore, the disclosure in these documents

does not raise serious doubts that IL-B50 antagonists and its effects on dendritic cells have a therapeutic effect in allergic diseases.

28. In a further line of argument, the appellant submitted that the disclosure in document D33 also questions the mechanism in the patent because, although it attributed a role to IL-B50 in the treatment of allergy, it revealed it to be independent of dendritic cells.

29. Document D33 discloses that, in a mouse model of gastrointestinal allergies, IL-B50 (TSLP) is required for allergic inflammation and that while its receptor on T cells was required to mediate a Th2 response, this was not the case for dendritic cells. However, this document does not show that the same conclusions can be drawn for other allergies and moreover does not provide any reasons to doubt that, for allergies involving dendritic cells, antagonists to IL-B50 would be suitable for treatment. Since the appellant's argument in relation to document D33 was submitted in the context of claims directed to the treatment of allergies involving the blocking of dendritic cell function, this disclosure does not support the appellant's argument since it does not concern allergic diseases involving dendritic cells.

30. In view of the above, the board is not persuaded that the invention as claimed is not sufficiently disclosed. The requirements of Article 83 EPC are fulfilled.

Novelty - Article 54 EPC

31. It was undisputed that document D1 formed part of the state of the art pursuant to Article 54(2) EPC for the

claimed subject-matter and disclosed the use of antibodies to IL-B50 receptor subunit Rδ2 in the context of allergy (see page 155, lines 19 to 20).

32. However, the respondent disputed that the document sufficiently disclosed the treatment of allergic diseases with these antagonists. Document D1 concerned a new cytokine receptor, designated as CRCGCL, which was identical to the IL-B50 receptor subunit Rδ2 in the patent. The passage on page 155, lines 19 to 20 read: "*In another specific embodiment, anti-CRCGCL antibodies of the invention are used to treat, prevent, modulate, detect and/or diagnose allergy and/or hypersensitivity.*". However, in the context of the document as a whole, the skilled person would have read this passage as a speculative therapeutic application of the antibodies.

33. The board agrees with the respondent in this respect for the following reasons.

33.1 In document D1, both antagonists and agonists of the receptor are mentioned as useful not only for the treatment of all the diseases listed in the paragraph bridging pages 8 and 9, cited by the appellant, but also for the treatment of completely unrelated diseases. Indeed, according to the passage entitled "Biological activities of CRCGCL", on page 140 and following, the receptor may be useful for controlling the proliferation, activation and maturation of B and T cells (page 141, lines 5 to 10). Diseases caused by a decrease in the level of receptor activity may be treated by administration of the receptor, and those caused by an increase may also be treated by administration of the receptor or an antagonist (page 143, second and third paragraphs). Examples of

diseases which may be treated by the receptor or antagonists to it are those caused by viruses, bacteria or fungi as listed on pages 143 to 145. Further diseases that may be treated by the receptor, its agonists or antagonists include hyperproliferative disorders, cardiovascular disorders and cancers (pages 161, 162 and 167). The passages referred to above list both agonists and antagonists of IL-B50 as being useful for the treatment of a list of unrelated diseases. In the board's view, the skilled person would have considered it unlikely that all listed diseases could be treated with the disclosed receptor subunit or its agonists or antagonists.

33.2 As concerns specifically the treatment of allergic diseases, reference can be made to various passages of document D1 in addition to that on page 155 cited by the appellant. The passage on page 149, lines 7 to 10, reads: "*Additionally, CRCGCL polypeptides or polynucleotides of the invention, agonists and/or antagonists thereof, may be used to treat, prevent, and/or diagnose IgE-mediated allergic reactions.*"; the passage on page 158, lines 26 to 29, reads: "*In specific embodiments, polynucleotides and/or polypeptides of the invention are used to treat or prevent chronic inflammatory, allergic or autoimmune conditions, such as those described herein or are otherwise known in the art.*"; finally, the passage on page 160, lines 29 to 31 reads: "*Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by CRCGCL polynucleotides or polypeptides, or agonists or antagonists of CRCGCL.*".

It is thus apparent that in document D1 both agonists and antagonists are intended for the treatment of

allergic diseases. The skilled person could not have derived from this which of the two would be suitable in the treatment of allergic diseases. The board considers the passage on page 148, which mentions that a receptor agonist can skew a patient's immune response to a Th2 response, not to be a disclosure of a mechanism of action of the receptor in any of the diseases listed and thus also not in allergic diseases. In fact, the disclosure of document D1 does not go beyond isolating CRCGCL, proposing that it is a member of the cytokine-receptor family and showing its expression on T cells. Therefore, which diseases the antagonists or agonists are suitable for treating is not directly derivable from document D1 (contrary to with the patent; see points 14. to 16. above). Thus, the passage does not change the information the skilled person would have derived from document D1 as a whole and does not teach how to modulate the receptor when the disease to be treated is an allergic disease.

34. The board thus comes to the conclusion that, on the basis of its disclosure as a whole, document D1 would not have disclosed to the skilled person that receptor subunit Rδ2 antagonists are suitable for treating allergies. The claimed subject-matter is thus novel with regard to the disclosure in document D1.

Inventive step - Article 56 EPC

35. The board considers that the appellant's argument questioning the suitability of the antibodies defined in the claims for the purpose of treating allergic diseases pertains rather to an assessment under Article 83 EPC (dealt with above in points 14. to 30.). Indeed, since the treatment of allergic diseases is the

therapeutic application already stated in the claims, the assessment of inventive step does not appear to require an analysis of whether such an effect is achieved by such antibodies. Accordingly, the board sees no need to elaborate further on this line of argument.

36. The appellant submitted that the claimed subject-matter did not involve an inventive step starting from the disclosures in documents D2 and D5. Accordingly, in view of the decision of the board (see further down), inventive step is assessed from both perspectives.

37. Document D5 reviews therapeutic strategies for treating allergic diseases and asthma (see title and abstract) and explains the mechanism underlying chronic allergic inflammation, as observed in asthma, allergic rhinitis and atopic dermatitis, characterised among other mechanisms by the mobilisation of effector cells into the tissues, driven by a complex mixture of cytokines and chemokines, including those secreted by Th2 cells (page 1037, first paragraph). The three strategies for therapy identified (i.e. prevention of T-cell activation, modulation of the Th1/Th2 balance to inhibit or prevent Th2-associated cytokine expression and inhibition of the effects of these cytokines, e.g. on IgE and eosinophils (see abstract)) unambiguously link Th2 cells, and cytokines secreted by them, to chronic allergic inflammation and allergic diseases. As a means to prevent T-cell activation, it lists, *inter alia,* antibodies to CD4, immunosuppressants inhibiting T-cell growth, and substances preventing the release of IL-4 and IL-5 from Th2 cells. As a means to modulate differentiation into Th1/Th2 cells, it lists administration of IFN-γ, IL-12 or IL-18 to induce activation of Th1 cells and antibodies to block the

effect of IL-4, IL-5, IL-9 and IL-13 (see Table 2 and page 1038, penultimate paragraph to page 1041, second paragraph).

38. The claimed subject-matter differs from this disclosure in that IL-B50 and its receptor are the targets for the treatment. The objective technical problem may thus be formulated as the provision of an alternative treatment for allergic diseases.

39. In a first line of argument, the appellant submitted that since document D1 would have taught the skilled person that Th2 responses were linked to the IL-B50 receptor and since the skilled person would have known that blocking the development of a Th2 response was a strategy to be considered in the treatment of allergic diseases, the claimed solution would have been obvious to the skilled person. Reference was made to the passage of document D1 on page 148 reading: "*CRCGCL agonists may be used as agents to* […] *direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response*".

40. However, in the context of novelty, the board has concluded that document D1 did not disclose the suitability of IL-B50 receptor antagonists for treating allergies (see point 34. above).

41. The board thus considers that the skilled person seeking to provide an alternative treatment for allergic diseases to the treatments listed in document D5 would not have found the claimed alternative suggested in document D1. Thus, the argument based on the disclosure in document D5 representing the closest prior art must fail.

42. Document D2 identifies IL-B50 as a new interleukin target in the network of cell interactions in the immune system. Claims 19 and 20 generally refer to IL-B50 agonists and antagonists in methods of modulating cell physiology or development, the antagonist optionally being an antibody binding to IL-B50. However, they do not disclose which cells will be the target of this modulation, and the IL-B50 receptor has not yet been identified (see paragraph bridging pages 48 and 49). Thus, document D2 fails to disclose in which interactions IL-B50 is involved. The document suggests the use of antagonist antibodies for blocking immune responses (page 39) and discloses that IL-B50 or its antagonists might be useful in treating, for example, immune disorders (paragraph bridging pages 13 and 14).

43. The claims are directed to therapeutic applications of antibodies to IL-B50, its receptor and the receptor subunits in the treatment of allergic diseases. This thus differs from the disclosure in document D2 in that it relates to a specific immune disease. The appellant accordingly formulated the objective technical problem when starting from the disclosure in document D2 as "to provide IL-B50 antibodies for use in an alternative immune disorder".

44. In the appellant’s view, document D2 itself would have provided the incentive to use antibodies to IL-B50 in the treatment of allergy. The appellant pointed to passages in document D2 (see pages 2 and 3) allegedly disclosing a role for mast cells in allergy-related disorders and the importance of B cells and T cells in immune responses. Document D2 would thus have provided an incentive to treat allergic diseases as claimed.

45. However, the board notes that document D2 does not as such concern mast cells and that the particular passages referred to by the appellant are disclosed in the "Background of the invention" section of document D2, which does not state that IL-B50 plays a role in any mechanism involving mast cells. The board is accordingly not convinced by the appellant's argument that the mention of mast cells in these passages would have motivated the skilled person to provide antibodies to IL-B50 as a solution to the technical problem.

46. Moreover, the appellant concludes from the fact that document D2 mentions in these passages mast cells together with B cells and T cells being important to the immune response that the skilled person would have considered allergy-related disorders as a solution to the problem. However, the board notes that emphasising particular cell types in the "Background of the invention" section of document D2 as important in the context of an immune response in general cannot be equated with a clear pointer to allergic disorders in particular. This line of reasoning is therefore not convincing.

47. In view of the above considerations, the board concludes that the claimed subject-matter would not have been obvious to the skilled person and accordingly involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of the claims of the main request, filed during the oral proceedings of 6 August 2020, and a description to be adapted thereto.

The Registrar: The Chair:

L. Malécot-Grob B. Claes

Decision electronically authenticated