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Datasheet for the decision of 24 June 2024

Case Number: T 0419/16 - 3.3.04

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Language of the proceedings: EN

Title of invention:
Use for Interleukin-33 (IL-33) and the IL-33 Receptor Complex

Patent Proprietor:
Merck Sharp & Dohme LLC

Opponents:
Regeneron Pharmaceuticals, Inc.
Strawman Limited
Gray, Tony
Takeda California, Inc.
Sanofi

Headword:
IL-33 antagonist antibody/MERCK SHARP & DOHME

Relevant legal provisions:
EPC Art. 87(1), 54, 56

Keyword:
Priority - (yes)
Novelty - auxiliary request 1 (yes)
Inventive step - auxiliary request 1 (yes)

Decisions cited:
G 0001/22, G 0002/22, T 0694/15, T 0419/16, T 0816/16, T 0261/19

Catchword:
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Case Number: T 0419/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 24 June 2024

Appellant: (Opponent 1)	Regeneron pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591-6707 (US)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Appellant: (Opponent 2)	Strawman Limited Orchard Lea Horns Lane Combe Witney, Oxfordshire OX29 8NH (GB)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Appellant: (Opponent 4)	Takeda California, Inc. 10410 Science Center Drive San Diego, CA 92121 (US)
Representative:	Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Appellant: (Opponent 5)	SANOFI 174, Avenue de France 75013 Paris (FR)
Representative:	Zwicker, Jörk ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)

Respondent: (Patent Proprietor)	Merck Sharp & Dohme LLC 126 East Lincoln Avenue Rahway, New Jersey 07065-0907 (US)
Representative:	Merck Sharp & Dohme LLC 120 Moorgate London EC2M 6UR (GB)
Party as of right: (Opponent 3)	Gray, Tony Middlemead Hook Hampshire RG27 9TE (GB)
Representative:	Avidity IP Broers Building Hauser Forum 21 JJ Thomson Avenue Cambridge CB3 0FA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 5 January 2016 concerning maintenance of the European Patent No. 1725261 in amended form**

Composition of the Board:

Chairman	B. Claes
Members:	A. Chakravarty
	L. Bühler
	O. Lechner
	M. Blasi

Summary of Facts and Submissions

I. Opponents 1, 2, 4 and 5 filed appeals against the interlocutory decision of the opposition division that, account being taken of the amendments in the form of auxiliary request 2, the European patent No. 1 725 261 and the invention to which it related, met the requirements of the EPC.

II. The patent proprietor is respondent to the appeals and opponent 3 is a party as of right to the proceedings.

III. The board has already issued interlocutory decision T 419/16 of 3 February 2022 in the case. In that decision, the board considered that the main request before it (auxiliary request 2 as found allowable by the opposition division) was not allowable since the subject-matter of claims 3 to 5 extended beyond the application as filed, contrary to Article 123(2) EPC (see point 20 of the Reasons).

In relation to auxiliary request 1, the board considered that claims 1 and 2 (the sole claims) met the requirements of Article 123(2) EPC and Article 83 EPC, but left the issues of novelty and inventive step undecided.

The board considered that the subject-matter of claims 1 and 2 of auxiliary request 1 related to the same invention as disclosed in the previous (priority) application. Because the board's decision on priority, novelty and inventive step hinged on the answer to questions referred to the Enlarged Board of Appeal in cases G 1/22 and G 2/22, the board decided to stay the proceedings until a decision was issued by the Enlarged

Board.

IV. The claims of auxiliary request 1 read:

"1. An antagonist of IL-33 for use as a medicament, wherein the antagonist comprises a binding composition from an antibody that specifically binds to IL-33.

2. The antagonist of Claim 1, wherein the binding composition from the antibody comprises:
a) a monoclonal antibody;
b) a humanized antibody; or
c) an [sic] Fab, Fv, or $F(ab')_2$ fragment".

These claims are identical to claims 1 and 2 of the main request (auxiliary request 2 as considered allowable by the opposition division).

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

D1: WO 2004/056868;

D3: Baekkevold E.S. *et al.*, Am. J. Pathol, 2003, 163(1), 69-79;

D4: Onda H. *et al.*, J. Cereb. Blood Flow & Metab., 1999, 19, 1279-1288;

D6: Coyle A.J. *et al.*, J. Exp. Med, 1999, 190(7), 895-902;

D10: US 6,323,334;

D42: WO 95/01997;

D79: O'Neill L.A.J. *et al.*, Immunology Today, 2000, 21(5), 206-209;

D80: Dunn E. *et al.*, Trends in Immunology, 2001, 22(10), 533-536.

VI. In its consolidated decision G 1/22 and G 2/22 of 10 October 2023, the Enlarged Board of Appeal provided the following answers to the referring board's questions:

"*I. The European Patent Office is competent to assess whether a party is entitled to claim priority under Article 87(1) EPC.*

There is a rebuttable presumption under the autonomous law of the EPC that the applicant claiming priority in accordance with Article 88(1) EPC and the corresponding Implementing Regulations is entitled to claim priority.

II. The rebuttable presumption also applies in situations where the European patent application derives from a PCT application and/or where the priority applicant(s) are not identical with the subsequent applicant(s).

In a situation where a PCT application is jointly filed by parties A and B, (i) designating party A for one or more designated States and party B for one or more other designated States, and (ii) claiming priority from an earlier patent application designating party A as the applicant, the joint filing implies an agreement between parties A and B allowing party B to rely on the priority, unless there are substantial factual indications to the contrary".

VII. The board issued a summons to a second oral proceedings together with a communication under Article 15(1) RPBA setting out its preliminary opinion on the remaining issues in the appeal case. It stated that the decision on novelty hinged on whether or not the disclosure in document D1 was comprised in the state of the art under Article 54 EPC, in particular on whether or not priority from US provisional patent application 60/545,730 was validly claimed. In relation to inventive step, the board was in preliminary agreement with the opposition division on the issue and referred to section 4 ff of the decision under appeal.

VIII. The appellants all informed the board in writing that they would not attend the scheduled oral proceedings. The board subsequently cancelled the oral proceedings and informed the parties that a decision would be issued in due course.

IX. The arguments of appellants relevant to this decision are summarised as follows.

Auxiliary request 1 - claims 1 and 2
Priority right (Article 87(1) EPC)

The respondent had acknowledged that neither the original assignment nor a certified copy of the assignment from the inventors and applicants of the US priority application to the PCT applicant could be provided. The failure to provide these documents had been due to company reorganisations and personnel changes in the relevant patent department. However, a lack of organisation was not an acceptable excuse and the documents filed by the respondent in place of the requested documents could not shift the burden of proof

from the respondent to the appellants of showing that a valid transfer had taken place.

Thus, for the claimed subject-matter the priority claimed from US 60/545,730 was not valid for reasons of lack of entitlement to the priority right. The effective date for the claimed subject-matter was thus 15 February 2005.

Novelty (Article 54 EPC)

Since the claimed subject-matter was not entitled to priority, document D1 belonged to the state of the art. The opposition division had correctly held that the disclosure in document D1 anticipated the claimed subject-matter relating to the treatment of arthritis. This objection also applied to the first medical use claim.

Inventive step (Article 56 EPC)

In the event that the claimed priority was valid, the claimed subject-matter lacked an inventive step over the disclosure in any of documents D6/D10, D3 or D4.

Starting from document D6 and/or D10 as the closest prior art

Documents D6 and D10 disclosed the treatment of allergic lung inflammation or asthma, respectively, with antibodies against ST2, an orphan receptor. Their disclosure was essentially equivalent. The sole distinguishing feature between the claimed subject-matter and the disclosure in documents D6/D10 was that a different molecule (IL-33) was antagonised. The objective technical problem to be solved was therefore

the provision of an alternative medicament. Alternatively, the problem to be solved could be seen as de-orphaning the T1/ST2 receptor in order to provide antibodies against its ligand.

The claimed subject-matter represented an obvious solution to either of these problems because the skilled person would have identified the ligand of the ST2 receptor molecule and used antagonistic antibodies to said ligand in medicine.

The skilled person had a profound knowledge of the sequence, structure and function of various other IL-1 family members. In particular, it was known (see e.g. documents D42, D79 and D80) that the members of the IL-1 family, e.g. IL-1β and IL-18 played an important role in diseases such as asthma, allergy and multiple sclerosis. The skilled person looking for the ligand of ST2 would have relied on approaches and methods routinely applied in the art (see e.g. documents D79 and D80) to identify ligands of an orphan receptor such as ST2, especially as this receptor belonged to the IL-1 receptor family and have arrived at the claimed subject-matter.

Starting from document D3 as the closest prior art

Document D3 disclosed that NF-HEV/IL-33 played a fundamental role in forming HEV-like vessels, which in turn were known to be causative for a number inflammatory and autoimmune diseases.

The difference between the disclosure in document D3 and the subject-matter of claim 1 was the use of an antagonistic NF-HEV/IL-33 antibody to inhibit IL-33 function in order to treat a medical condition. The

objective problem solved by the claimed subject-matter was the provision of therapeutic approaches based around NF-HEV (IL-33).

The claimed antibody for use in medicine was obvious because the state of the art suggested that NF-HEV was linked to specific diseases and indicated that the inhibition of NF-HEV would be therapeutically useful. Document D3 disclosed that chronic inflammation, rheumatoid arthritis, inflammatory bowel disease, nasal allergy and chronic skin diseases were linked to the endothelial cells of the high endothelial venules in which NF-HEV was highly expressed (page 69, right column, second full paragraph). This could only be understood by the skilled person as a strong hint to a causative link between IL-33 and these conditions.

The aim of document D3 was the identification of the factor or factors responsible for the formation/ maintenance of HEVs and HEV-like vessels. Document D3 concluded that NF-HEV may be involved in the regulation of the HEV phenotype, i.e. the differentiation of endothelial cells into HEVs (see abstract, last sentence). Although NF-HEV was characterised as a protein capable of localising to the nucleus of HEVs, its presence was also observed in vesicles in the cytoplasm reminiscent of secretory vesicles, which was clearly visible in Figure 3A. In view of the foregoing considerations, the claimed subject-matter lacked an inventive step in the light of the disclosure in document D3 alone.

Alternatively, the claimed subject-matter lacked an inventive step over the disclosure in document D3 in combination with common general knowledge. Starting from document D3, and in an alternative to the problem

above, the objective problem could be seen as the provision of an antagonist of NF-HEV.

The claimed solution was obvious because the skilled person would have realised that antagonistic antibodies against NF-HEV represented a solution to the problem because NF-HEV was known to be at least in part secreted and thus easily accessible to antibodies to antagonise its function.

Even if the skilled person had considered that NF-HEV was an intracellular protein, targeting it with an antibody would have been obvious because it was known from documents D90 to D92 that antibodies could enter living cells and specifically bind and inactivate intracellular proteins.

Starting from document D4 as the closest prior art

Document D4 related to the canine DVS 27 (= IL-33) in inflamed tissues in autoimmune diseases, suggesting it as a possible target for the treatment of these diseases. The immunochemical experiments demonstrated the *in vivo* and *in vitro* suitability of IL-33 as a target for an antibody. Thus, the skilled person starting from the disclosure in document D4 would, by making minimal structural modifications, have arrived at the claimed subject-matter.

X. The arguments of the respondent relevant to this decision are summarised as follows.

Auxiliary request 1 - claims 1 and 2
Priority right (Article 87(1) EPC) and novelty (Article 54 EPC)

The claimed subject-matter was entitled to priority and were thus unaffected by the disclosure in document D1.

Inventive step (Article 56 EPC)

The invention was based on the surprising finding that IL-33 was the endogenous ligand for the orphan receptor ST2. Although ST2 signalling had already been associated with a range of Th2-mediated disorders, the patent taught that its ligand was a cytokine (IL-33) and credibly proposed a therapeutic utility for IL-33 antagonists and agonists. The claimed subject-matter was not obvious regardless of whether the closest prior art related to ST2 or IL-33.

Starting from document D6 (and document D10) as the closest prior art

The disclosures in documents D6 and D10 were equivalent and related to the biology of the ST2 receptor. Specifically, they disclosed that effective reduction of allergic lung inflammation and airway hyper-responsiveness could be achieved using an anti-ST2 monoclonal antibody (mAb) (figure 5). Both document D6 and document D10 were concerned with treating immune and inflammatory conditions and both disclosed an orphan receptor and the real-world problem of looking for its endogenous ligand (if there was one), in order to develop alternative treatments for the same conditions.

IL-33 had not been identified as the ST2 ligand. Neither document suggested that ST2 activity could be modulated using modulators of IL-33 as there was no suggestion in the state of the art that IL-33 (aka NF-HEV), disclosed in document D3 or D4, was the relevant endogenous ligand.

Appellant-opponent 4's argument that the skilled person would have used the biostatistical methods disclosed in documents D79 and D80 to arrive at the invention was wrong because these documents did not show how the skilled person would have made the connection between ST-2 and NF-HEV without knowledge of the invention.

Starting from document D3 as the closest prior art

Document D3 disclosed a nuclear factor (NF-HEV) from high endothelial venules (HEVs). This protein was later shown to be identical to IL-33. Document D3 classified NF-HEV as a nuclear factor, i.e. an intracellular molecule, but did not identify it as a cytokine. HEVs were found in lymphoid tissues and HEV-like vessels (which might or might not be the same as HEVs) were seen in chronically inflamed non-lymphoid tissue, rheumatoid arthritis, IBD, nasal allergy, and various chronic skin diseases.

Document D3 was silent on whether or not the occurrence of IL-33 in HEV-like vessels was associated with the diseases where the HEVs were found. Although it was disclosed that NF-HEV "*was an attractive candidate for mediation of the cytokine effects that induce HEV-specific genes*", this did not mean that antagonists or agonists of NF-HEV could treat diseases. In order to reach such a conclusion, the skilled person would first have had to determine whether mediation of NF-HEV had

any effect on HEVs and then find out if this had any therapeutic outcome. Moreover, document D3 did not indicate whether an agonist or antagonist would be needed to treat any particular condition.

Document D3 disclosed that the skilled person faced the problem of "*investigating the biological role of NF-HEV in the nucleus and its functional role in HEV differentiation*" (see page 77, last paragraph). However, addressing this problem would not necessarily have led to any therapeutic outcome.

Thus, the claimed invention was not obvious starting from the disclosure in document D3.

Starting from document D4 as the closest prior art

Document D4 disclosed a cDNA encoding a protein identical to IL-33. The corresponding gene, DVS 27, was the most highly upregulated gene in vasospastic arteries of canine two-haemorrhage models. It concluded that the nuclear protein encoded by DVS 27 could be involved in inflammatory events, even though its functional role was unknown (see penultimate paragraph), but did not disclose whether DVS 27 protein was either causative of inflammation, a product of inflammation or part of a compensatory process resulting from inflammation. The information in document D4 was thus insufficient to allow the skilled person to conclude that an antagonist of DVS27 protein could treat inflammation.

There was no suggestion in document D4 that modulators of the DVS 27 protein should be identified for potential therapeutic use.

The requests of the parties

XI. Appellant-opponents 1, 4 and 5 as well as opponent 2 (party as of right) request that the decision under appeal be set aside and that the patent be revoked in its entirety.

Appellant-opponent 4 also requests that the documents designated D83 and D84 (EP 0 003 062 A1 and EP 0 004 810 A2 underlying decisions T 128/82 and T 36/83, respectively) be admitted into the proceedings.

Opponent 3 (party as of right) did not submit any requests in the appeal proceedings.

XII. The respondent requests that the appeals be dismissed (main request), or, alternatively, that the patent be maintained in amended form based on the set of claims of auxiliary requests 1 or 2, both filed with the reply to the statements of grounds of appeal.

Reasons for the Decision

Summary of the matters decided by the board in the interlocutory decision T 419/16 of 3 February 2022

1. In its interlocutory decision, the board decided:

"*1. Opponent 2's appeal is rejected as inadmissible and the request for reimbursement of the appeal fee is rejected.*

2. The appeal proceedings are stayed until a decision is issued by the Enlarged Board of Appeal in cases

G 1/22 and G 2/22. They will be continued in writing thereafter."

2. On substantive matters, the board considered the main request (auxiliary request 2 underlying the decision under appeal). It held that the subject-matter of claims 3 to 5 of the main request extended beyond the content of the application as filed, contrary to Article 123(2) EPC. Thus the main request was not allowable (see point 20 of the Reasons). This issue is *res judicata*.

3. In relation to auxiliary request 1, the board decided that claims 1 and 2 met the requirements of Article 123(2) EPC and Article 83 EPC. These issues are also *res judicata.* This left the issues of novelty and inventive step undecided.

4. On the subject of novelty, the board noted that the disclosure in document D1, published after the priority date but before the filing date of the patent, would, in the absence of a valid priority, anticipate the subject-matter of claim 1.

5. In relation to the validity of the claimed priority, the board decided that the subject-matter of claims 1 and 2 of auxiliary request 1 related to the same invention as disclosed in the previous application in the sense of Article 87(1) EPC. This issue is also *res judicata*.

6. A further objection of the appellants in relation to the validity of the claimed priority was whether or not a valid transfer of the right to claim priority from US provisional patent application 60/545,730 had taken place prior to the filing of PCT application, published

as WO 2005/079844. Because the board's decision on this issue hinged on an answer to questions referred to the Enlarged Board of Appeal in cases G 1/22 and G 2/22, the board decided to stay the proceedings until a decision was issued by the Enlarged Board.

Admittance of documents

7. No decision on the admittance or otherwise of documents the admittance/non-admittance of which was requested by the parties need be taken because none of these documents is relied upon in this decision.

Auxiliary request 1 - claims 1 and 2

The claimed subject-matter

8. Claim 1 is a claim pursuant to Article 54(4) EPC, i.e. it relates to a first medical use. The product is an IL-33 antagonist which comprises a binding composition from an antibody that specifically binds to IL-33. The purpose given in the claim is "for use as a medicament". The board also notes that according to the patent, the claimed antagonist is useful specifically in the treatment of "*a disorder or condition selected from the group consisting of asthma; allergy; multiple sclerosis; or arthritis*" (see paragraph [0011] and claim 4 of the patent as granted). Claim 2 is dependent on claim 1 and further defines the binding composition.

9. Under Article 54(4) EPC, a substance or composition is novel if it has not yet been used in a method referred to in Article 53(c) EPC (see also Case Law of the Boards of Appeal of the European Patent Office, 10th edition 2022, I.C.7.1.1).

Priority right (Article 87(1) EPC)

Summary of filings and applicants

10. The patent was granted on European patent application No. 05 713 577.4 (the "application") which was filed as a application No. PCT/US2005/004743 on 15 February 2005 published as WO 2005/079844(the "PCT application"). Priority was claimed from the US provisional patent application No. 60/545,730, filed on 17 February 2004 (the "priority application").

11. The priority application was filed in the name of J. Schmitz, M. Oft and R. Kastelein, the inventors. The international application was filed naming Messers Schmitz, Oft and Kastelein as inventors and, for the US, as inventors/applicants. For all designated States except the US, it names Schering Corporation as applicant. The published PCT application reflects this information. Mr J. Bazan was added under Rule 92*bis*.1 PCT as applicant and inventor for the US only by Form PCT/IB/306.

12. The European patent names Schering Corporation as applicant and Messers Schmitz, Oft, Kastelein and Bazan as inventors.

13. In consolidated decision G 1/22 and G 2/22 the Enlarged Board of Appeal decided that entitlement to claim priority (and any related assignments of priority rights) should be assessed under the autonomous law of the EPC (see Reasons 86). Furthermore, the Enlarged Board decided that there is a rebuttable presumption under the autonomous law of the EPC that the applicant claiming priority in accordance with Article 88(1) EPC

and the corresponding Implementing Regulations is entitled to claim priority (see Order I).

14. This presumption applies in the factual situation of the case at hand, where the European patent application derives from a PCT application and where the priority applicant(s) are not identical with the subsequent applicant(s). Furthermore, in the situation, as in the present case, where the PCT application (see point 10.) was jointly filed by parties A and B, (i) designating party A (here Messers Schmitz, Oft, Kastelein and Bazan) as inventors and applicants for the United States of America (US) only) and party B (here Schering Corporation for all designated States except the US), and (ii) claiming priority from an earlier patent application (here US provisional patent application No. 60/545,730) designating party A as the applicant, the joint filing implies an agreement between parties A and B, allowing parties B to rely on the priority, unless there are substantial factual indications to the contrary (see Order II).

15. Appellant-opponent 5 argued that, contrary to the opposition division's finding in the decision under appeal, there had been no valid transfer of the right to claim priority from US 60/545730 prior to the filing of the international application PCT/US2005/004743. Appellant-opponent 5 based this objection on the reason that the transfer had not been proven by the respondent in a formal way.

16. In view of the Enlarged Board of Appeal's decision that the joint filing of the PCT application implies an agreement between parties A and B, allowing party B to rely on the priority, the above objection cannot succeed because there is no requirement under the EPC

that a transfer of priority right be proven in a formal way.

17. Furthermore, there are no substantial factual indications brought forward by the appellants that could lead to the conclusion that the joint filing of the PCT application did not imply an agreement between the applicants of the US priority application and Schering Corporation as the co-applicant of the subsequent PCT application (for all states other than the US). Thus, the presumption that Schering Corporation was entitled to the priority right as regards earlier application US 60/545730 was not rebutted, and the claimed priority is not invalid for reasons of lack of entitlement to the priority right.

18. In conclusion, the priority claimed from US provisional patent application No. 60/545,730 as regards the subject-matter of claims 1 and 2 is valid.

Novelty (Article 54 EPC)

19. In the decision under appeal, point 4.6, the opposition division held that, in the absence of a valid priority, document D1 was relevant state of the art for subject-matter referring to treatment of arthritis with IL-33 antagonists (claims 4d, 10, 12d) and that therefore such subject-matter was not novel.

20. However, this objection is contingent on document D1 being part of the state of the art for the claimed subject-matter. Since it is not, and no other novelty-objection has been raised by the appellants, the board must conclude that the claimed subject-matter is novel.

Inventive step (Article 56 EPC)

21. Claims 1 and 2 of auxiliary request 1 are identical to the same claims of the main request, i.e. auxiliary request 2 before the opposition division. The opposition division held that the subject-matter of claims 1 and 2 would not have been obvious to the skilled person when starting from the disclosure in document D6 representing the closest prior art, considered either alone or in combination with the disclosure in documents D3 or D4.

22. Claim 1 is for an IL-33 antagonist binding composition from an antibody that specifically binds to IL-33, for use as a medicament (see point 8.). The patent discloses that it is useful specifically in the treatment of "*a disorder or condition selected from the group consisting of asthma; allergy; multiple sclerosis; or arthritis*" (see paragraph [0011] and claim 4).

Closest prior art

23. The opposition division came to a positive decision on inventive step, assessed solely when starting from the disclosure in document D6 representing the closest prior art. The appellants however consider the disclosure in several (different) documents (documents D3, D4 or D6/D10) as starting points for assessing inventive step.

24. Although assessing inventive step only from one closest prior art disclosure may constitute an efficient approach to address the situation where multiple similar disclosures were presented as starting points for the assessment of inventive step, it is, however,

not an appropriate approach if the alternative starting points represent alternative and different routes to the invention, as they do in the case at hand. In such a situation, each starting point needs consideration because under Article 56 EPC, in order for an inventive step to be acknowledged, the claimed invention must not be obvious to a skilled person having regard to the state of the art, i.e. any prior art disclosure with the exclusion of documents under Article 54(3) EPC (see T 694/15, Reasons 13 to 15, T 816/16, Reasons 3.7.1 and T 261/19, Reasons 2.5).

Starting from document D6 and/or D10 as the closest prior art

25. Document D6 discloses a study of T1/ST2 (ST2), an orphan receptor of unknown function, expressed on the surface of murine T-helper type 2 cells (Th2) (see abstract). It reports the results of experiments, *inter alia* using an anti-ST2 mAb demonstrating that ST2 "*is a crucial cell-surface receptor that is required for Th2 effector responses*" (see page 896, left column, first full paragraph) and plays an important role in Th2-mediated inflammatory responses (see abstract). Disclosed is that ST2 may prove to be a novel target for the selective suppression of Th2 immune responses (*ibid*). Document D6 neither discloses that ST2 is the receptor for IL-33 nor any anti-IL-33 antibody that antagonises its activity or a medical use for an anti-ST2 antibody or for an anti-IL-33 antibody.

26. The disclosure in document D10 does not go beyond or is equivalent to that in document D6. The board therefore refers to document D6 only, but the same considerations apply equally for document D10.

27. The most similar product disclosed in document D6 to the claimed antibody is an anti-ST2 mAb (*ibid*). However, no general or specific medical use is disclosed for this antibody. The difference between this and the claimed antibody is the target (ST2/IL-33 receptor) and its medical use(s) both in general and the specific uses identified in the description of the patent (treating asthma, allergy, multiple sclerosis and arthritis).

28. The objective technical problem that arises out of the above differences and their technical effects can be formulated as the provision of a medicament, e.g. for treating asthma, allergy, multiple sclerosis and arthritis.

29. The appellants argue that the identification of IL-33 as the ligand of ST2 was an obvious solution to the objective technical problem of either providing of an alternative medicament or alternatively, the de-orphaning of the Tl/ST2 receptor in order to provide antibodies against its ligand. However, neither of these formulations is appropriate, since they are not derived from the difference between the claimed subject-matter and the disclosure in document D6 and the technical effects related to the difference.

30. The board however agrees with the conclusion on obviousness set out in the decision under appeal (see point 4.8), that, while undertaking a search for the ST2 ligand might have been desirable for the skilled person, it was however not known:

- what the ligand would be;
- what its specific biological functions would be; and

- whether (either agonistic or antagonistic) antibodies to the, as yet unknown, ligand could reasonably be expected to be useful as therapeutic agents.

31. There is no pointer in the disclosure in document D6 that would have motivated the skilled person to undertake the rather substantial research project of trying to identify the unknown ligand for the ST2 as a route to solving the above formulated problem and which could have directed the skilled person to the claimed invention.

32. The appellants' argument that the skilled person starting from document D6 would have had the incentive and the means to identify the then unknown ligand to ST2, especially because ST2 shared structural similarities with the IL-1 receptor family, is not relevant to the assessment of obviousness in the case in hand because it fails to take into account that identifying the ligand of ST2 was not the objective technical problem to be solved as formulated in point 28.

33. In conclusion, the claimed invention was not obvious to the skilled person starting from the disclosure in document D6 (and document D10) representing the closest prior art.

Starting from document D3 as the closest prior art

34. Document D3 concerns the identification of a protein, designated NF-HEV, from HEVs, which was later found to be identical to IL-33. NF-HEV was identified as a bipartite nuclear localisation signal which "*may be one of the key nuclear factors the controls the specialised*

HEV phenotype" (see abstract).

35. The differences between the disclosure in document D3 and the claimed subject-matter are that the claim is for an antibody capable of antagonising IL-33 (NF-HEV) and that this antibody is useful in medicine.

36. In view of these differences and their technical effects, the objective technical problem to be solved starting from document D3 may be formulated as the provision of a medicament, e.g.for treating asthma, allergy, multiple sclerosis and arthritis.

37. The question to be answered in assessing obviousness is whether or not the skilled person starting from the disclosure in document D3 and seeking a solution to the problem set out above, would have arrived at the claimed subject-matter.

38. The board answers the question in the negative. Although document D3 identifies NF-HEV as a nuclear factor from HEVs, it does not disclose how this relates to treatment of disease. It is recognised that HEV-like vessels are found in a number of diseases (IBD, nasal allergy and various chronic skin diseases; see page 69, left column), but it is neither suggested that NF-HEV might be a therapeutic target nor that its action should be antagonised. At most document D3 can be considered suggesting a therapeutic role for NF-HEV in the statement "*is an attractive candidate for mediation of the cytokine effects that induce HEY-specific genes*" (see page 77, left column), made in connection with elucidating the function of NF-HEV. This disclosure does not however equate with predicting a utility. The board thus agrees with the respondent that it would not have provided the skilled person a

reasonable expectation that antagonists of NF-HEV would be suitable for treating diseases.

39. Appellant-opponent 4 argued that document D3 explicitly taught that IL-33/NF-HEV may control intensification and maintenance of chronic inflammation (see sentence bridging pages 69 and 70), thus complementing the statements in documents D6 and D10 concerning the role of the IL-33 receptor (ST2) in inflammatory conditions.

40. However, this argument fails because, as noted in point 25. above, there is no disclosure in document D6 that directly links the then orphan receptor ST2 to the nuclear factor NF-HEV, later identified as IL-33. Thus, without the aid of hindsight, the skilled person would not have connected the disclosure of ST2 in documents D6 and D10 with the disclosure in document D3 of the nuclear factor NF-HEV.

Starting from document D4 as the closest prior art

41. Document D4 discloses the identification of genes that are differentially expressed in vasospastic arteries of canine two-haemorrhage models. A full-length cDNA for the unknown clone DVS 27, whose expression was upregulated the most, was isolated. This corresponding gene was later identified as encoding (canine) IL-33.

42. The disclosure in document D4 is technically further away from the claimed invention than that in document D6. In fact, it discloses that "*Although its functional role still is unknown, the DVS 27 gene was found to encode a nuclear protein that could be involved in inflammatory events. Thus, such an approach will be useful, at least in part, to predict the role of proteins encoded by the unknown genes*" (see page

1287, left column). This disclosure cannot be understood as a suggestion to the skilled person that an antibody capable of antagonising the encoded protein would be useful as a medicament. The skilled person thus would not have arrived at the claimed subject-matter.

Summary

43. Having considered all of the appellants' lines of argument on inventive step, starting from documents D6/D10, D3 and D4, the board concludes that the claimed subject-matter was not obvious to the skilled person at the effective date of the patent.

44. There were no further objections as regards the claims of auxiliary request 1 to be considered by the board. The claims are thus allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form with the following claims, and a description and drawings to be adapted thereto as necessary:

claims 1 and 2 of auxiliary request 1, filed with the respondent's reply to the statements of grounds of appeal.

The Registrar: The Chair:

I. Aperribay B. Claes

Decision electronically authenticated