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Case Number: T 2570/11 - 3.3.04

Application Number: 04798568.4

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Language of the proceedings: EN

Title of invention:
Method for the treatment of multiple sclerosis by inhibiting IL-17 activity

Patent Proprietor:
UCB Pharma, S.A.

Opponents:
01: Eli Lilly & Co.
02: Merck Serono S.A.
03: Schering Corporation
04: Genentech, Inc.

Headword:
IL-17 inhibition/UCB

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:
-

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Case Number: T 2570/11 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 12 July 2017

Appellant: (Patent Proprietor)	UCB Pharma, S.A. Allée de La Recherche 60 1070 Brussels (BE)
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Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 28 September 2011 revoking European patent No. 1687026 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Claes
	L. Bühler

Summary of Facts and Submissions

I. The appeal of the patent proprietor (hereinafter "appellant") is directed against the decision of the opposition division to revoke European patent No. 1 687 026 having the title "*Method for the treatment of multiple sclerosis by inhibiting IL-17 activity*".

Claim 1 of the patent as granted read:

"1. The use of an inhibitor of IL-17 activity for the manufacture of a medicament for the treatment and/or prophylaxis of multiple sclerosis (MS) wherein the inhibitor is an IL-17R:Fc fusion protein or an antibody or functionally active fragment thereof which binds to IL-17 or IL-17R."

II. Four oppositions were filed against the patent invoking Article 100(a) EPC in combination with Articles 54 and 56 EPC, and Articles 100(b) and 100(c) EPC as grounds of opposition. The opposition division revoked the patent because the subject-matter of claim 1 of the patent as granted (main request) lacked an inventive step (Article 56 EPC). This finding also applied to the six auxiliary requests.

III. With the statement of grounds of appeal, the appellant argued that the subject-matter of claim 1 of the patent as granted (main request) involved an inventive step and submitted an auxiliary request and a number of new documents.

IV. Opponent 01 (hereinafter "respondent I"), opponent 02 (hereinafter "respondent II") and opponent 04

(hereinafter "respondent VI") responded to the appeal within the time limit set.

V. With a letter dated 18 July 2016 the appellant withdrew the auxiliary request (see section III).

VI. One month prior to the date of oral proceedings, the appellant replied to the respondents' submissions and filed five new auxiliary requests as well as a number of further new documents.

Claim 1 of the First Auxiliary Request differed from claim 1 as granted (see section I) in that the inhibitor was defined as "(a) an IL-17R:Fc fusion protein or (b) an antibody or functionally active fragment" (emphasis added by the board).

Claim 1 of the Second Auxiliary Request differed from claim 1 as granted (see section I) in that the wording "an IL-17R:Fc fusion protein or" was deleted.

Claim 1 of the Third Auxiliary Request differed from claim 1 as granted (see section I) in that the wording "and/or prophylaxis" was deleted.

Claim 1 of the Fourth Auxiliary Request combined the amendments of the First and Third Auxiliary Requests, whereas claim 1 of the Fifth Auxiliary Request combined the amendments of the Second and Third Auxiliary Requests.

VII. The duly summoned respondents I, III and IV announced that they would not be attending the oral proceedings.

VIII. Oral proceedings before the board were held as scheduled. Respondents I, III and IV were not present,

as announced. At the end of the oral proceedings the chairwoman announced the board's decision.

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

D2: Matusevicius *et al.* (1999), Vol. 5, p. 101-104.

D4: Lubbers *et al.* (2001), J. Immunol., Vol. 167, p. 1004-1013.

D6: Zhang *et al.* (2003), J. Immunol., Vol. 170, pages 2153 to2160.

D14: Lock *et al.* (2002), Nature Medicine, Vol. 8, No. 5, p. 500-508.

D19: Haak *et al.* (2009), J. Clin. Investigation, Vol. 119, No. 1, pages 61 to 69.

D21: Özenci *et al* (2002), Multiple Sclerosis, Vol. 8 pages 396 to 404.

D59: Declaration of Dr. Mark Christie dated 8 February 2010

D83: The Cytokine Handbook (Fourth Edition), 2003, Eds. Thomson and Lotze, in particular pages 486 to 497.

D85: Trajkovic *et al*. (2001), J. Neuroimmunol., Vol. 119, pages 183 to 191.

X. The arguments of the appellant in relation to inventive step (Article 56 EPC) and relevant for the present decision can be summarised as follows:

All requests - claim 1

There was no disclosure in document D2 of a therapeutic treatment for multiple sclerosis (MS). Accordingly, starting from the disclosure in document D2 the problem to be solved was - appropriately formulated - the provision of means for treating MS.

Although it examined IL-17 mRNA levels in cells related to MS, document D2 also recognised that these levels did not necessarily correlate with protein levels in the same cells because cytokine expression was often regulated at the post-transcriptional level (see page 103, right-hand column, lines 20 and 21). It could therefore not be concluded from the results in document D2 whether or not the IL-17 protein was up-regulated in MS patients.

The level of knowledge in the art relating to the cytokine network was not nearly enough to make predictable the effect of inhibiting cytokines such as IL-17. In contrast to the respondents' view, a mere observed "*correlation*" or "*nexus*" between a cytokine and MS did not establish that cytokine as a causative agent of MS or as a target for effective therapy.

Document D21, a review article published three years after document D2 was published, reflected the common general knowledge on the immensely complicated and poorly understood "*cytokine puzzle*" in the context of MS. The document focused on various cytokines with a putative role in MS, whereby TGFβ, IL-4, IL-13 and IL-15 were particularly singled out as interesting for further study. The document was silent on IL-17 and warned that "*in the evaluation of the possible role of a certain cytokine in MS pathogenesis, determination of*

cytokine levels yield, at best, incomplete information and must be supplemented by studies of additional factors that contribute to the effects of the cytokine" (see page 402, left-hand column, lines 29 to 30 and 45 to 49). The authors of document D21 thus did not consider that from the data disclosed in document D2, IL-17 could be considered a credible validated target for treatment of MS, let alone conclude on a role of IL-17 in MS. This was noteworthy since some authors of D2 and D21 were from the same research group.

Document D2 related to experimental results which were not significantly relevant (see page 103, left-hand column, lines 22 to 27; sentence bridging both columns on page 103 and sentence bridging page 103 and 104), qualified statements about a possible role of IL-17 in MS as "*hypothetically*" (see page 104, left-hand column, lines 13 to 15) and recognised that "*effects of increased levels of IL-17 in MS are not known*" (see page 104, left column, last paragraph of the discussion). A flaw in the disclosure in document D2 was that no cerebrospinal fluid (CSF) data were available for the healthy control group.

Even if IL-17 was up-regulated in MS, then the skilled person could not derive from document D2 whether IL-17, in the context of MS, was a "*good*" or a "*bad*" cytokine. Furthermore, assuming that IL-17 was up-regulated and a bad cytokine, document D2 did not test IL-17 or an IL-17 inhibitor in any relevant animal model and thus did not shed light on the role of IL-17 in the cytokine puzzle of MS, let alone made it obvious that inhibition of IL-17 or IL-17 receptor provided a genuine target for an effective treatment for MS.

Also the knowledge that the cytokine was "pro-inflammatory" did not establish inhibition thereof as an effective MS treatment. Indeed, inhibition of the cytokine TNF-α, which was known in the art as a pro-inflammatory cytokine with damaging effect in MS - and whose levels were consistently increased in the CSF of patients with MS and whereby patients with active MS have higher circulating and CSF levels of TNF-α than patients with stable disease - had failed as a treatment for MS in two clinical trials as it resulted in an exacerbation of MS (see e.g. post-published document D59).

Even if the person skilled in the art had a reasonable expectation of success that the inhibition of IL-17 activity would provide a method for the treatment of MS, then the available test methods would not have revealed the effects as observed in the patent in suit since they were based on short term models only.

The experiments disclosed in the patent applied two particular forms of the experimental autoimmune encephalomyelitis (EAE) mouse reflecting as closely as possible MS in humans. The first model was a relapsing-remitting model (see examples 2 and 3) which allowed the identification of a molecule that substantially reduced relapsing or chronic disease when administered after the onset of disease. The second, a "chronic", model (see Example 4) allowed therapeutic dosing of the test inhibitor during established disease, but did not exhibit a relapsing-remitting cycle. The choice of the relapsing-remitting model enabled the observation that inhibition of IL-17 nearly obliterated relapses in the later stages of the disease, but had negligible effects on the early phase of the disease which was the one typically targeted in the "acute" MS models commonly

used in the art. These models exhibited only one phase of disease and did not reach a chronic or relapsing-remitting state (see e.g. document D6, Figure 1; document D14, Figures 4 and 5 and document D19, Figures 3A, 4A and 6).

Document D4 related to anti-IL-17 antibodies in the treatment of rheumatoid arthritis, which was a different disease than MS. The combination of the disclosure in document D2 with that in document D4 was accordingly not appropriate.

XI. The respondents' arguments in relation to inventive step and relevant for the present decision can be summarised as follows:

All requests - claim 1

IL-17 was a pro-inflammatory cytokine known to induce inflammatory responses as well as the expression and secretion of various cytokines and chemokines. It was known to be produced, in humans, almost exclusively by activated $CD4^+$ memory T-cells (see patent paragraph [0002] and e.g. document D2, page 101, left-hand-column, lines 12 to 30, page 104, left-hand column, lines 3 to 27).

The aim of the experiments disclosed in document D2 was to detect and enumerate mononuclear cells (MNC) expressing IL-17 mRNA in blood and cerebrospinal fluid (CSF) samples of MS patients. The samples came from MS patients experiencing clinical exacerbation and clinical remission as well as from control individuals (page 101, right-hand column, lines 10 to 14). The purpose of document D2 was thus to validate a new target for the treatment of MS.

The major findings in document D2 were that (1) the number of MNCs expressing IL-17 mRNA was higher in CSF samples as compared to samples from peripheral blood of MS patients; (2) the number of MNCs expressing IL-17 mRNA was higher in blood samples of MS patients as compared to blood samples from healthy individuals; (3) the number of MNCs expressing IL-17 mRNA was 3.5 fold higher in blood samples of MS patients during exacerbation as compared to the number in multiple sclerosis patients during remission; and (4) the number of MNCs expressing IL-17 mRNA had a tendency to increase in CSF of MS patients during exacerbation as compared to the number in MS patients during remission.

Document D2 thus established a link between the pro-inflammatory cytokine IL-17 selectively expressed in MNCs, a subset of T-cells vital for MS pathogenesis, and MS, possibly with respect to the exacerbation phase of the disease as evidenced by the fact that IL-17 transcripts augmented during the relapsing (exacerbation) phase (see page 104, left-hand column, lines 3 to 27).

Furthermore, although document D2 acknowledged that the mechanism by which IL-17 may act in MS was not known (page 104, left-hand column, lines 15 to 17) it pointed out in particular that, since IL-17 triggered the expression of pro-inflammatory cytokines and chemokines, that "*Increased IL-17 levels may thus be involved in the migration and activation of autoaggressive T-cells in the CNS*" (see page 104, left-hand column, lines 17 to 23).

In its final paragraph, the conclusion of the article, document D2 linked the production of IL-17 from activated memory T-cells with relapses in MS. This was

logical in view of the fact that these cells (i) were fundamental in induction and maintenance of MS and its experimental model EAE (see e.g. document D84) and (ii) could be autoreactive T-cells prone to reactivation, leading to exacerbation, and of the fact that IL-17 expressing MNCs augmented during exacerbation.

Thus, the teaching in document D2 of an increased number of IL-17 mRNA-expressing MNCs in the blood of MS patients, and particularly in patients experiencing relapses, would give the skilled person more than a hope of succeeding in treating the disease by inhibiting IL-17 activity with either an antibody or a IL-17R:Fc fusion protein, both means to inhibit IL-17 activity belonging to the common general knowledge, or at least a strong motivation to try to do it.

Although, document D2 did not disclose a treatment or prophylaxis of MS with antibodies or fusion proteins, the factual difference between the disclosure in document D2 and the subject-matter of claim 1 was that claim 1 provided standard means for inhibiting the target validated in document D2, namely IL-17.

Accordingly, starting from the teaching in document D2, the problem to be solved by the claimed subject-matter was the provision of means for inhibiting IL-17 as a validated target for treating MS.

The solution was the use of an inhibitor of IL-17 activity as defined in claim 1 of the patent in suit. This solution was however obvious to the skilled person at the effective date of the invention, based on D2 in combination with the common general knowledge.

Antibodies to IL-17 and its receptor (IL-17R) and IL-17R:Fc fusion proteins were known in the art for inhibiting IL-17 activity and had been successfully used to reduce inflammation in animal models of inflammatory diseases (see e.g. patent paragraph [0003] and document D4 abstract and page 1006, right-hand column, lines 9 to 42).

Document D85 elucidated a mechanism by which IL-17 may act in MS. It disclosed that, in *in vitro* cultures, IL-17 synergised with other pro-inflammatory cytokines (IFN-γ, IL-1, TNF-α) to activate inducible nitric oxide synthase (iNOS) and thus potentiated NO production in rodent astrocytes (see item 3.1 on pages 186 to 187 and; item 3.4 on pages 188-189) and directly linked the action of IL-17 in the CNS with a damage thereof. It concluded that "*our study suggests an important role for IL-17-activated astrocytes in tissue destruction during inflammatory T cell-mediated CNS diseases such as MS*" (page 190, left-hand column, lines 9 to 12) and referred to treatment of MS which involved IL-17 when it stated that "*one could be tempted to speculate that neutralization of IL-17 with subsequent inhibition of astrocyte, but not macrophage NO synthesis, would presumably preserve beneficial immunosuppressive effect of NO in lymphoid organs, while preventing its destructive action in the CNS*" (page 190, left-hand column, lines 4 to 9).

Thus, a skilled person, based on the teachings of document D2 in combination with the disclosure in document D85 would be prompted to use an inhibitor (e.g. a neutralising antibody or a receptor:Fc fusion protein) in order to inhibit a cytokine directly involved in a destructive process in CNS, and notably in MS, and thus would have arrived at the solution to

the technical problem with a reasonable expectation of success.

The subject-matter of claim 1 thus lacked an inventive step.

XII. The requests of the parties were the following:

The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained as granted (main request), or, alternatively, that the patent be maintained according to one of the first to fifth auxiliary request filed with letter dated 12 June 2017.

Respondent I, II and IV requested that the appeal be dismissed. Respondent III did not file any requests.

Reasons for the Decision

1. The appeal is admissible.

2. Respondents I, III and IV were duly summoned to the oral proceedings before the board, but did not attend. In accordance with Rule 115(2) EPC and Article 15(3) RPBA the proceedings were continued in their absence. These parties were considered as relying on their written cases.

Inventive Step (Article 56 EPC)

Main Request - claim 1 (as granted)

3. The claimed subject-matter is in the form of a Swiss-type medical use claim, the therapeutical agent being "an inhibitor of IL-17 activity", e.g. an antibody

binding to IL-17 or its receptor and the therapeutic indication being multiple sclerosis (MS; see section I).

Closest prior art

4. To assess whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal apply the "problem and solution" approach, which involves the identification of the closest prior art, the formulation of the objective problem to be solved in view of the closest prior art and the effects achieved by the claimed invention and its solution.

5. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in the prior art providing a promising springboard towards the claimed invention, being normally a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention (Case Law of the Boards of Appeal of the European Patent Office, 8th edition 2016, I.D.3.1).

6. In the appeal proceedings the parties have highlighted three documents which qualified in their view to represent the closest prior art, *i.e.* documents D2, D4 and D14, whereby the latter was selected by the opposition division and preferred by the appellant.

7. After having heard the parties during the oral proceedings on the issue, the board concluded that the closest prior art was represented by either document D2 or document D14, rather than document D4. The parties were subsequently heard on inventive step starting from each of these documents.

8. In view of the outcome of its decision in relation to the assessment of inventive step based on document D2 representing the closest prior art (see further) - which the board considers to provide ample reasons as to why this document constitutes a "promising springboard" to the claimed invention, if not the "most promising springboard" - and in view of the fact that, as recognised in the case law of the boards of appeal, more than just one prior art document could qualify, according to the circumstances, as starting point for the problem solution approach, the board considers it unnecessary for the purposes of the present decision to embark on a detailed analysis of whether - as argued by the appellant - the disclosure in document D14 was, according to the criteria developed by the boards of appeal, closer to the claimed invention, since this would not, in any case, rule out the disclosure in document D2 as a suitable starting point for the problem solution approach. Moreover, the board notes that the determination of the closest prior art hinges on the assessment of what document D2 directly and unambiguously conveys to the person skilled in the art, which is a point of dispute between the parties.

9. Document D2 has the title "*Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis*" and assesses the involvement of interleukin-17 (IL-17) in MS. The disclosed experiments aim at determining, by means of *in situ* hybridisation (ISH) with synthetic oligonucleotide probes, IL-17 mRNA expression in mononuclear cells (MNC) in peripheral blood and cerebrospinal fluid (CSF) of *inter alia* patients with clinically definite MS, which were either in clinical exacerbation (defined in the document as a "s*udden appearance of new, or worsening of previously present* ,

neurological symptoms and signs, lasting > 24 h and occurring within 1 month before examination"; see page 101, right-hand column, last paragraph) or remission. In addition to the MS patients, three control groups were examined composed of (i) patients suffering from aseptic meningoencephalitis (AM), (ii) patients with other non-inflammatory neurological diseases and (iii) healthy patients, whereby CSF was available only from the MS and AM patients (see page 102, left-hand column, lines 1 to 14).

10. The main results obtained in document D2 are depicted in Table 1 and summarised by the authors in the abstract (see lines 5 to 10) as follows: "*Numbers of IL-17 mRNA expressing blood MNC were higher in patients with MS and acute aseptic meningoencephalitis (AM) compared to healthy individuals. Higher numbers of IL-17 mRNA expressing blood MNC were detected in MS patients examined during clinical exacerbation compared to remission. Patients with MS had higher numbers of IL-17 mRNA expressing MNC in CSF compared to blood. This increase in numbers of IL-17 mRNA expressing MNC in CSF was not observed in patients with AM. Our results thus demonstrate increased numbers of IL-17 mRNA expressing MNC in MS with higher numbers in CSF than blood, and with the highest numbers in blood during clinical exacerbations*" (emphasis added by the board). At the end of the paper it is concluded from these results that the "*effects of increased levels of IL-17 in MS are unknown, but an induction of the production of proinflammatory cytokines and chemokines may be one mechanism by which IL-17 could contribute to the inflammatory brain damage in MS*" (see page 104, left-hand column, lines 33 to 38).

11. The board is thus satisfied that the skilled person would derive from the disclosure of document D2 that it identifies a correlation between the clinical appearance of MS and the expression of interleukin-17, particularly intrathecally in CSF, but also systemically in peripheral blood of MS patients. Even if the document does not identify IL-17 as the causative agent of MS, the skilled person would derive from it that IL-17 plays an important role in MS and that MS was an IL-17 related disorder. The board is accordingly satisfied that document D2 identifies and validates the pro-inflammatory cytokine IL-17 (see patent in suit paragraph [0002]) as a potential drug target for therapeutic strategies in the treatment of MS.

The technical problem to be solved

12. The difference between the teaching in document D2 and the claimed subject-matter is that the treatment of MS is not specifically disclosed in the document. Accordingly, in agreement with the appellant and consistent with the technical problem as formulated in the patent (see paragraph [0011]), the board considers that the technical problem can thus be formulated as the provision of means for the treatment of MS.

13. The solution to this problem as claimed is to use "an inhibitor of IL-17 activity [...] wherein the inhibitor is an IL-17R:Fc fusion protein or an antibody or functionally active fragment thereof which binds to IL-17 or IL-17R".

14. The claimed subject-matter is in the form of a Swiss-type medical use claim (see section I and point 3

above), i.e. a claim of which attaining the claimed therapeutic effect is a functional technical feature.

15. Accordingly, when assessing the obviousness of the claimed subject-matter it has to be determined whether or not the skilled person, starting from the teaching in document D2 would have arrived at the claimed solution in an obvious way.

Obviousness

16. As noted in point 11, above, document D2 establishes IL-17 as a potential drug target for therapeutic strategies in the treatment of MS. Accordingly, the board is satisfied that the experimental teaching in document D2 would motivate the skilled person to establish the effects of inhibiting IL-17 activity in MS in the reasonable expectation of successfully reducing adverse effects of the observed correlation between the clinical appearance of MS and the expression of IL-17. In other words, it justified a legitimate expectation of the skilled person that blocking of IL-17 signalling would exhibit a therapeutic effect for MS, even if not a curative one.

17. The tools for establishing the effects of inhibiting IL-17 activity in MS, i.e. animal models and IL-17 inhibitors were readily available to the skilled person in the art.

18. Indeed, paragraph [0003] of the patent establishes that: "*Inhibitors of IL-17 activity are well known in the art, for example an IL-17R:Fc fusion protein was used to demonstrate the role of IL-17 in collagen-induced arthritis* (ref. to document D4) *and neutralising polyclonal antibodies have been used to*

reduce peritoneal adhesion formation (...). Neutralising monoclonal antibodies are commercially available (R&D Systems UK)". Similarly statements are made in paragraph [0015] of the patent. Document D4 discloses the successful use of antibodies to IL-17 and its receptor (IL-17R) and IL-17R:Fc fusion proteins inhibiting IL-17 activity to reduce inflammation in animal models of inflammatory diseases (see e.g. abstract and page 1006, right-hand column, lines 9 to 42).

19. As regards animal models, the patent further establishes that also these were known in the art, i.e. it states in paragraph [0053]: *"A number of different models of MS are known in the art ('t Hart and Amor 2003, Current opinion in Neurology, 16:375-83). In particular, experimental autoimmune encephalomyelitis (EAE) in ABH mice is considered to be a relevant model for MS in humans (Baker et al., 1990. Journal of Neuroimmunology, 28:261-270). Both acute and relapsing remitting models have been developed*."

20. Accordingly, the board considers that the skilled person would have arrived at the solution as formulated in claim 1 in an obvious manner.

21. The appellant has submitted a number of arguments questioning the credibility of the experimentation and the results disclosed in document D2 and leading to doubts as to their predictive value when assessing obviousness of the claimed invention. Accordingly, it was argued that the skilled person would not derive from the prior art that IL-17 or its receptor was a promising therapeutic target in MS. The appellant further argued that in view of the particular animal

models used for testing, the subject-matter of claim 1 should be held non-obvious.

Is up-regulation of the IL-17 protein in MS disclosed in document D2?

22. A first line of argument submitted by the appellant was that the experiments disclosed in document D2 examined cellular IL-17 mRNA rather than protein levels. It was stated in document D2 that mRNA expression levels did not necessarily correlate with protein levels in the cells, in particular in relation to cytokines for which it was well known that often their expression was regulated at the post-transcriptional level (see page 103, right-hand column, lines 20 and 21). It could therefore not be concluded from the results of the experiments disclosed in document D2 whether or not the IL-17 protein was up-regulated in MS patients.

23. The whole passage from which the appellant cites reads (page 103, right-hand column, lines 16 to 27): "*ISH is a highly sensitive and specific method to evaluate cytokine production at the cellular level, without the limitations and drawbacks intrinsic for methods used to detect circulating cytokines in body fluids. Cytokine mRNA expression is, however, not necessarily identical to cytokine protein production. Tumor necrosis factor-α (TNF-α) gene expression is for instance regulated at both transcriptional, posttranscriptional and translational levels. On the other hand, a good correlation between mRNA and protein levels have been reported for IL-10 and TNF-α in MS.*" (emphasis added by the board)

24. Thus, the passage discloses that, generally, cytokine mRNA expression is not necessarily identical to cytokine protein production, i.e. it may or may not be identical. It gives one example, i.e. in relation to TNF-α, where no such correlation may be found. In the last sentence of the passage, reference is made to two publications, where, in the context of the involvement of particular cytokines in particular in MS, a correlation had been found, in relation to TN-α and another cytokine IL-10. In the board's view, the passage as a whole suggests to the skilled person that in MS a good correlation exists between mRNA and the protein levels of cytokines, be it that they are not always "*identical*".

25. The board notes furthermore that that results of the experiments in document D2 are not presented as levels of expression of IL-17 mRNA in MNC, but rather as the number of such cells detected to express IL-17 mRNA. Consequently, whether or not there is a direct correlation between the expression and protein production is therefore not of primary interest in this context, but rather the amount of expressing cells.

26. Finally, the board observes that, despite being careful (see point 23 above), the authors of document D2 themselves infer a correlation between IL-17 mRNA and protein levels. Indeed, in the paragraphs following the cited one the authors report about their findings on IL-17 mRNA expression in MNCs and then conclude in the final paragraph of the document on page 104: "*In conclusion, increased numbers of IL-17 mRNA expressing MNC were observed* [...]. *Higher numbers of IL-17 mRNA expressing blood MNC were detected* [...]. *The effects of increased levels of IL-17 in MS are not known, but an induction of the production of proinflammatory*

cytokines and chemokines may be one mechanism by which IL-17 could contribute to the inflammatory brain damage in MS". Note the distinction made between IL-17 mRNA levels and IL-17 levels.

27. In conclusion, the skilled person would not disregard the value of the obtained results and declare them worthless, but would rather consider that they disclose a correlation between IL-17 mRNA and protein expression, i.e. that IL-17 is up-regulated in the the tested MS patients.

Was the role of IL-17 in the "cytokine puzzle" understood?

28. A second line of argument submitted by the appellant was that it constituted common general knowledge of the skilled person that the so-called "cytokine puzzle", referring to the cytokine network, in the context of MS was immensely complicated and poorly understood. Indeed, document D21 for example, a review publication on the subject, referred to a putative role of a large number of different cytokines in MS, but did not, however, mention IL-17 in this context. Nor did they refer to document D2.

29. Furthermore, document D21, emphasised that "*in the evaluation of the possible role of a certain cytokine in MS pathogenesis, determination of cytokine levels yield, at best, incomplete information and must be supplemented by studies of additional factors that contribute to the effects of the cytokine*" (see page 402, lines 29 to 30 and 45 to 49). The authors of document D21 thus did not consider that IL-17 could be considered as a validated target for treatment of MS or as playing a role in MS. Consequently, also document D2 could not be considered to provide such a disclosure.

30. Also document D2 qualified any statements about a possible role of IL-17 in MS as "*hypothetically*" (see page 104, left-hand column, lines 13 to 15) and recognised that "*effects of increased levels of IL-17 in MS are not known*" (see page 104, left column, last paragraph of the discussion).

31. The board acknowledges that, at the relevant date of the patent, the involvement of diverse cytokines in MS pathogenesis was not completely understood. This was indeed also confirmed in document D2 in the first paragraph: "*Cytokines produced by infiltrating cells as well as resident cells in the brain are currently believed to regulate immune responses in MS. The cytokine network in MS is, however, not fully elucidated.*" (page 103, right-hand column, lines 4 to 7). However, the board is satisfied that, despite this consideration, the skilled person would consider the disclosure in document D2 to contribute to the elucidation of the MS cytokine network rather than to merely take stock of its complexity (see also points 8 to 10 above).

32. A similar consideration applies to the lack of reference to document D2 in the review document D21 and the consequential allegation that the skilled person would not have considered document D2 to disclose IL-17 as a validated target for treatment of MS, let alone to conclude on a role of IL-17 in MS. The board refers in this context to other disclosures contained in the prior art which do acknowledge the work of document D2. Indeed, document D14, entitled "*Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis*" (see page 502, left hand column, lines 22 to 24), document D83, being part of the book "The Cytokine Handbook"

under the heading "*IL-17 in autoimmune disorders/ Multiple sclerosis*" (see page 495, left hand column, lines 9 to 14) and document D85, entitled "*Interleukin-17 stimulates inducible nitric oxide synthase activation in rodent astrocytes*" (see page 183, right-hand column, lines 18 to 22) all explicitly refer to the results of the experiments disclosed in document D2. Moreover, the lack of reference to document D2 in document D21 and the silence on IL-17 is no evidence that the authors of document D21 disapproved of the results reported in document D2. The focus of document D21 is also a different one as it proposes reasons for the discrepancies of results reported on cytokines in MS. Therefore, the board can not accept that the absence of a reference to this document in document D21 would discredit the value of the results disclosed in document D2.

Was it known that IL-17 was a "bad" cytokine?

33. In a third line of argument the appellant submitted that the skilled person could not derive from document D2 whether IL-17, in the context of MS, was a "good" or a "bad" cytokine, i.e. whether its presence had a positive or negative effect on MS.

34. In reply the board refers to its considerations in paragraph 25 above and particularly notes again the last half-sentence of document D2: "*[...] but an induction of the production of proinflammatory cytokines and chemokines may be one mechanism by which IL-17 could contribute to the inflammatory brain damage in MS.*" In the board's opinion, the skilled person would have perceived in view of the disclosure of document D2 that IL-17 is, in the words of the appellant, a "bad" cytokine.

Could in the absence of proper testing IL-17 be identified as a drug target?

35. In a fourth line of argument it was submitted that even if it was assumed that IL-17 was a "bad" cytokine, document D2 did not shed light on its role in the cytokine puzzle of MS, let alone made it obvious that inhibition of IL-17 or IL-17 receptor provided a genuine target for an effective treatment for MS seeing that neither IL-17 nor an IL-17 inhibitor had been tested in, e.g., a relevant animal model.

36. The board refers to points 8 to 10 above where reasons were given as to why, even in the absence of actual testing of an inhibitor, the skilled person would have derived from document D2 that IL-17 was a promising target for MS treatment.

Was the knowledge that IL-17 was a pro-inflammatory cytokine sufficient to identify it as a drug target in MS?

37. In a fifth line of argument the appellant submitted that even the knowledge that IL-17 was a "pro-inflammatory" cytokine would not establish an effective MS treatment. Indeed, inhibition of the cytokine TNF-α, which was known in the art as a pro-inflammatory cytokine with damaging effect in MS - whose levels were consistently increased in the CSF of MS patients with MS and patients with active MS having higher circulating and CSF levels of TNF-α than patients with stable disease - had failed as a treatment for MS in two clinical trials as it resulted in exacerbation of MS (see e.g. post-published document D59).

38. As far as the failure of an anti-TNF-α therapy for MS is concerned, the board concurs with the respondents

that TNF-α is not IL-17 and that failure of a MS therapy based on one validated target for treatment of MS, here TNF-α, would not prevent the skilled person from persisting and to consider testing other validated targets for the treatment of MS, here IL-17.

39. In the context of the first aspect of the argument, the board refers to paragraph [0002] of the patent in suit, which itself confirms that IL-17 was known in the art as a pro-inflammatory cytokine which stimulates the secretion of a wide range of other cytokines from various non-immune cells. Hence, the board considers that the skilled person would take this knowledge into account when contemplating the teaching of document D2.

Were the animal models used in the patent for testing particular?

40. In a sixth line of argument the appellant submitted that the available methods for testing were based on short term models which would not have revealed the effects observed in the patent. Only by using the particular models used by the inventors over an extended period of time could the specific effects of IL-17 on MS be detected.

The experiments disclosed in the patent applied two particular forms of the experimental autoimmune encephalomyelitis (EAE) mouse reflecting as closely as possible MS in humans. The first model was a relapsing-remitting model (see examples 2 and 3) which allowed the identification of a molecule that substantially reduced relapsing or chronic disease when administered after the onset of disease. The second chronic model (see Example 4) allowed therapeutic dosing of the test

inhibitor during established disease, but did not exhibit a relapsing-remitting cycle.

Only the choice of the relapsing-remitting model enabled the observation that inhibition of IL-17 nearly obliterated relapses in the later stages of the disease although the same had negligible effects on the early phase of the disease. This was the phase which was typically targeted in the commonly used "acute" MS models which exhibited only one phase of disease.

41. Firstly, the board notes in this context that the appellant has not argued that the particular experimental autoimmune encephalomyelitis (EAE) mouse models used in the patent were not known to the person skilled in the art. In fact, in relation to the relapsing-remitting model reference is made in the patent to a publication of the year 1990 (see paragraphs [0088]) and in relation to the chronic model to a publication from 2004 (see paragraph [0109]), therefore confirming that both models were available to the skilled person.

42. In contrast to the appellant's submission that, the fact that at least the use of the relapsing-remitting model was not uncommon, may also be taken from paragraph [0053] of the patent (see point 18, above). Thus, the board is not convinced by the argument that the skilled person would normally have used an acute model and consequently would have missed the particular effects of an inhibition of IL-17.

43. In this context, the board refers also to Figure 10 of the patent, relating to example 4 in which a chronic MS model is used, which demonstrates a clear therapeutic effect of the tested antibodies also at the onset of

the disease, i.e. in the acute phase. Thus, even by using an acute model the effects would have been seen by the skilled person.

Would the skilled person have dismissed using the tools disclosed in document D4?

44. The appellant also submitted that since document D4 relates to anti-IL-17 antibodies in the context of the treatment of rheumatoid arthritis, which was a different disease than MS, the skilled person would not consider using such compounds in the context of the treatment of MS.

45. However, the board sees no merit in this argument since it neither establishes that the skilled person specialised in MS would be unaware of or would refrain from considering using therapeutic tools known for rheumatoid arthritis, nor establishes the reason why the skilled person would refrain from using the compounds disclosed in document D4 in the context of MS.

Conclusion

46. In summary, the skilled person, intending to provide means for the treatment of MS, would be prompted by the disclosure in document D2 which establishes IL-17 as a potential drug target for the treatment of MS, to test inhibiting IL-17 activity in MS. The skilled person would have all the necessary tools to proceed since animal models for MS were available as were antagonistic IL-17 antibodies, which had already been successfully tested as therapeutics for other diseases (see document D4).

47. Therefore, the subject-matter of claim 1 does not fulfil the requirements of Article 56 EPC. Hence, the main request is not allowable.

First to Fifth Auxiliary Requests - claim 1

48. It has not been argued by the appellant that the amendments to claim 1 in the First to Fifth Auxiliary Requests (see section VI) would remedy the deficiency of lack of inventive step in relation to claim 1 of the main request.

49. Also the board sees no reason why the negative findings of the board on inventive step of the subject-matter of claim 1 of the main request would not apply to the subject matter of claim 1 of the auxiliary requests.

50. Therefore,t claim 1 of these requests lacks an inventive step. Hence, none of the five Auxiliary Requests is allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated