Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 8 June 2017

Case Number: T 1113/11 - 3.3.04

Application Number: 98937834.4

Publication Number: 1004315

IPC: A61K39/395

Language of the proceedings: EN

Title of invention:
Preventives and/or remedies containing anti-IL-6 receptor neutralizing antibodies for reducing the excretion of urinary protein in systemic lupus erythematosus

Patent Proprietor:
Chugai Seiyaku Kabushiki Kaisha

Opponent:
Ablynx N.V.

Headword:
Preventives/CHUGAI

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 1113/11 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 8 June 2017

Appellant: (Patent Proprietor)	Chugai Seiyaku Kabushiki Kaisha 5-1, Ukima 5-chome, Kita-ku Tokyo, 115-8543 (JP)
Representative:	Wakerley, Helen Rachael Reddie & Grose LLP The White Chapel Building 10 Whitechapel High Street London E1 8QS (GB)
Respondent: (Opponent)	Ablynx N.V. Technologiepark 21 9052 Ghent-Zwijnaarde (BE)
Representative:	Vlassak, Katrien Ablynx NV Technologiepark 21 9052 Zwijnaarde (BE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 10 March 2011 revoking European patent No. 1004315 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 against the decision of the opposition division to revoke European patent No. 1 004 315. The title of the patent is "*Preventives and/or remedies containing anti-IL-6 receptor neutralizing antibodies for reducing the excretion of urinary protein in systemic lupus erythematosus*".

Claim 1 of the patent read:

"1. Use of an anti-interfeukin-6 (IL-6) [*sic*] receptor antibody that neutralizes the biological activity of IL-6 in the manufacture of a medicament for reducing the excretion of urinary protein in systemic lupus erythematosus."

II. The opposition division held that, whereas the invoked grounds for opposition in Article 100(a) EPC (concerning novelty under Article 54 EPC) and Articles 100(b) and (c) EPC did not prejudice the maintenance of patent, the subject-matter of claim 1 lacked inventive step (Article 100(a) EPC concerning inventive step (Article 56 EPC)).

III. In the statement of grounds of appeal the appellant argued in favour of an inventive step of the subject-matter of claim 1 of the patent and filed a number of documents.

IV. With its reply to the appeal the opponent (hereinafter respondent) stated that it maintained all the objections raised in the opposition proceedings and filed arguments in support of lack of novelty

(Article 54 EPC) and inventive step (Article 56 EPC) in respect of the subject-matter of claim 1.

V. After the parties had been summoned to oral proceedings, both the appellant and the respondent announced that they would be neither present nor represented during the oral proceedings.

VI. Oral proceedings took place in the absence of the parties. At the end of the oral proceedings the chairwoman announced the decision.

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

D2: WO 96/12503

D6: Malide *et al.* (1995), Human Pathology Vol. 26, pages 558-564.

D10: Kiberd (1993), Journal of the American Society of Nephrology, Vol. 4, No. 1, pages 58-61.

D13: Finck *et al.* (1994), The Journal of Clinical Investigation, Vol. 94, pages 585-591.

D27: Spronk *et al.* (1992), Clinical and experimental immunology, Vol. 90, pages 106 -110.

D28: Ryffel *et al.* (1994), The American Journal of Pathology, Vol. 144, pages 927-937.

D29: Gijbels *et al.* (1995), Mol. Med., Vol. 1, pages 795-805.

A9: Swaak *et al.* (1989), Rheumatol. Int., Vol. 8 pages 263-268.

A10: Metsärinne *et al.* (1992), Rheumatol. Int., Vol. 12: 93-96.

A11: Heremans *et al.* (1992), Eur. J. Immunol., Vol. 22, pages 2395-2401.

A12: Wendling *et al.* (1993), J. Rheumatol., Vol. 20, pages 259-262;

A13: Mihara *et al.* (1991), Immunol., Vol. 74, pages 55-59.

A15: Ozmen *et al.* (1995), Eur. J. Immunol., Vol. 25 pages 6-12.

VIII. The appellant's arguments in relation to inventive step (Article 56 EPC) that are relevant for the present decision may be summarised as follows:

The patent provided *in vivo* animal studies with NZB/W F1 mice, a model strain with the closest known pathology to systemic lupus erythematosus (SLE). The use of anti-interleukin-6 receptor (anti-IL-6R) antibodies which neutralised the biological activity of interleukin-6 (IL-6) was highly effective at reducing proteinuria and also prolonging the life of the tested mice.
Document D13 described the treatment of the same type of mouse with anti-IL-6 antibody. Administration led to a suppressive effect on the development of significant proteinuria, at least for an initial seven months after the start of the treatment (see Figure 4), to an increase of anti-DNA antibodies (see Figure 3) and to

an improvement in survival compared with control mice, *i.e.* with 90% of the treated mice being alive after nine months compared with 30% of mice administered a control agent (see Figure 5). Treatment with anti-IL-6 antibody did not significantly reduce the serum levels of immunoglobulin (Ig) in treated mice (see Table 1). Document D13 provided no experimental data showing the effect of anti-IL-6 antibody on levels of IL-6 per se (either serum levels or otherwise), provided no evidence that IL-6 signalling was blocked, and did not empirically address the mechanism by which a reduction in proteinuria was achieved using the anti-IL-6 antibody.

Document D13 used anti-IL-6 antibody to reduce proteinuria in SLE, while the claimed invention used anti-IL-6 receptor (anti-IL-6R) antibody.

The technical effect resulting from this difference was the significant reduction in proteinuria (see Figure 1) and increased survival rates (see Figure 2), both for a longer duration than in document D13. Serum levels of IgG1, IgG2 and IgG3 (but not IgM or IgA) were decreased in mice treated with anti-IL-6R antibody compared with mice administered saline only (see Table 1). Serum levels of IgG and IgM anti-DNA antibodies did not rise significantly in control mice treated with saline (unlike the control mice in document D13), but levels of IgG anti-DNA antibodies were significantly reduced in the mice treated with anti-IL-6R antibody (see Figure 3). Serum concentrations of IL-6 in mice treated with anti-IL-6R antibody were below the level of detection (see paragraph [0153] of the patent).

The patent demonstrated that anti-IL-6R antibodies had a **more potent effect** than anti-IL-6 antibodies in the treatment of SLE as evidenced by improved survival rates, the reduction of serum immunoglobulins and the suppression of serum levels of IL-6 in treated mice. Furthermore, there was a marked decrease in the occurrence of proteinuria compared to control mice: only one of ten treated mice developed significant proteinuria (i.e. > 100 mg/dl) after 64 weeks, compared with the saline-treated mice which all developed nephritis after 54 weeks (see Figure 1 and paragraph [0150] of the patent). This was a notable improvement over the findings in document D13 after nine months (about 39 weeks) of treatment, when 30% of the mice treated with anti-IL-6 antibody had developed significant proteinuria (see Figure 4).

Accordingly, the objective technical problem was the provision of an alternative and/or improved agent for reducing the excretion of urinary protein in SLE.

The claimed invention was not obvious to the skilled person for at least one of the following reasons:

Document D10 taught away from the invention as it disclosed that rat anti-IL-6R receptor antibody was not able to reduce the excretion of urinary protein in SLE, *i.e.* the treatment of animals of a particular murine lupus nephritis model with a rat anti-IL-6R antibody had no evident favourable effect on proteinuria (see page 60, left-hand column, "Discussion"), and the reduction of anti-DNA antibody levels (a common characteristic of SLE patients) using anti-IL-6R antibodies did not correlate with a reduction in proteinuria.

Document D10 considered it "*difficult to determine whether more favourable effects would have resulted if neutralizing antibodies and/or the progressive increase in plasma IL-6 failed to occur*" (sentence bridging pages 60 and 61). Accordingly, whether tolerisation, *i.e.* blocking of the mouse immune response to the rat antibody (e.g. by anti-CD4 antibodies) would lead to a favourable effect on proteinuria was purely speculative.

In fact, from document A15 the skilled person knew that the treatment of NZB/W F1 mice with a rat anti-IFN-γ receptor antibody inhibited the onset of glomerulonephritis and the development of proteinuria (see Table 1), despite the mice not being tolerised to the rat antibody. Accordingly, prior tolerisation was not essential to show a reduction in proteinuria through treatment of mice with a rat antibody.

At the relevant date, the prior art cast doubt on whether an agent which disrupted the IL-6 pathway could provide a useful therapy for SLE. From document D27 it was known that IL-6 had no pathogenic role in the generation of IgG and/or anti-DNA antibodies before exacerbations or manifestations appeared in SLE sufferers (see "Abstract", page 109, right-hand column, first and final paragraph). Also, document D28 disclosed that treatment with anti-IL-6 antibody of NZB/W F1 mice, *i.e.* the same as used in document D13 and the patent in suit, did not prevent the spontaneous development of glomerulonephritis and that it was thus unlikely that increased IL-6 production played a role in the pathogenesis of lupus nephritis (see Abstract). Also in documents A9 and D10 no relationship was found between serum levels of IL-6 and the course of SLE or

its symptoms, except in a minority of patients (see page 265, right-hand column, first paragraph).

Although the authors of document D13, as the rationale for their study, suspected IL-6 of promoting lupus-like autoimmune disease (see page 585, "Introduction", last sentence), the IL-6 levels were not measured in mice treated with anti-IL-6 antibody.

Accordingly, the skilled person would not have considered that modulation of the IL-6 pathway, in particular using an anti-IL-6 receptor antibody, was a suitable alternative to the use of anti-IL-6 antibody, as taught in document D13, for reducing the excretion of urinary protein in SLE.

Documents A11 to A13 and D29 demonstrated that treatment of mice with anti-IL-6 antibody was associated with markedly increased serum levels of IL-6 (see documents A11 to A13 "Abstract", document D29, page 798, right column, fourth paragraph and page 801, right column, final paragraph). Thus, administration of a neutralising anti-IL-6 antibody to mice was expected to increase the biological activity of IL-6 *in vivo*.

IX. The respondent's arguments in relation to inventive step (Article 56 EPC) that are relevant for the present decision may be summarised as follows:

Document D13 represented the closest prior art. It investigated the role of IL-6 in a mouse SLE model by administration of a rat derived mAb reactive with IL-6. Treatment with this mAb prevented production of anti-DNA antibodies, significantly reduced proteinuria and prolonged life. Only mice that were made tolerant to the rat anti IL-6 mAb by administration of anti-CD4

concurrent with the first dose of anti-IL-6 mAb showed an inhibition of the renal manifestation of the disease, *i.e.* proteinuria (see Figure 4). Document D13 thus showed that IL-6 promoted SLE and that the blocking of IL-6 signalling (through inhibition of the IL-6/IL-6R interaction) reduced the renal manifestation of SLE, *i.e.* lupus nephritis and its symptom (the excretion of urinary protein).

The claimed invention used anti-IL-6 receptor antibody instead of anti-IL-6 antibody. The problem to be solved was the provision of an alternative agent for blocking IL-6 signalling in SLE.

Document D2 provided an alternative agent for prevention of or therapy of diseases caused by IL-6 production, *i.e.* an IL-6R antibody, which blocked signal transduction by IL-6 and inhibited the biological activity of IL-6 (see page 3, lines 5 to 8 and Reference Example 2). The antibody was further effective in reducing a histological form of lupus nephritis, mesangial proliferative glomerulonephritis, and in reducing the concomitant excretion of urinary protein (see Example 1). Document D2 disclosed that IL-6 levels in the blood did not increase upon treatment with the IL-6R antibody (page 8, lines 3 to 5).

Accordingly, modulation of the IL-6 pathway, in particular using anti-IL-6R antibody, was a suitable and obvious alternative to the use of anti-IL-6 antibody, disclosed in document D13, for reducing the excretion of urinary protein in SLE.

Document D10 confirmed the teaching in document D13 that the blocking of IL-6 signalling reduced excretion

of urinary protein in SLE. The anti-IL-6R antibody therapy had favourable effects on renal function and structure (see Table 1 and "DISCUSSION" on page 60). Reduction of the renal manifestation of SLE, lupus nephritis, was however obtained with a *rat* anti-IL-6R antibody if and only if the mouse immune response to the antibody was blocked, i.e. the mice were tolerised. Table 1 actually showed that proteinuria was decreased in mice treated with an anti-IL-6R antibody (REC) as compared to mice treated with an IgG that did not bind IL-6R (IgG). Hence, blocking of IL-6 signalling in fact led to a reduction.

The mice in document D10 received the rat anti-IL-6R antibody without prior tolerisation, leading to the development of high titer neutralising antibodies to the anti-IL-6R antibody (see page 60, left-hand column, last two sentences of "RESULTS") which may interrupt any further effect of the anti-IL-6R antibody on proteinuria. Similar results were obtained in document D13 for non-tolerant mice receiving a rat anti-IL-6 antibody (see Figure 4). Accordingly, the skilled person would have understood that prior tolerisation of the mice to the rat antibody should be undertaken.

Document A15 was silent on the possible appearance of antibodies to the rat anti-IFN-γ antibody used to inhibit the onset of glomerulonephtritis and on a delay in the development of proteinuria in NZB/W F1 mice even though the mice used were not tolerised to the antibody. It was thus not clear whether, in this study, an anti-rat immune response was evoked by the rat antibody or not. However, a different pathway (blocking of IFN-γ) and thus a totally different mechanism of action were investigated in this study, and the treatments referred to schedules which were not the

same. Document A15 did not cast doubt on the conclusion in document D13 that administration of an antibody that blocked IL-6 signalling could reduce the renal manifestation of SLE, lupus nephritis, if, and only if the mouse immune response was blocked.

The skilled person could not conclude from document D27 that modulation of IL-6 signalling would or would not be a useful therapy to reduce the excretion of urinary protein in SLE, because the document was silent on the role of IL-6 in causing the renal SLE manifestation excretion of urinary protein. The document furthermore reported that, at the time of maximum disease activity during exacerbation, the plasma concentrations of IL-6 in all subgroups of SLE (and thus not only for lupus nephritis) were increased. The authors concluded that elevated concentrations of IL-6 in patients with SLE were a secondary phenomenon only because they found a lack of correlation of the rise in anti-DNA with the rise in IL-6 plasma concentrations (rises in anti-dsDNA tended to precede rises in IL-6). This in fact showed that, as early as 1992, the involvement of IL-6 in SLE was acknowledged. In addition from document D6 (see "Discussion") it was known that, in lupus nephritis, localised, site specific, intrarenal release of IL-6 may connect immunologic and inflammation events involved in progressive tissue damage in the kidney. The dilution of this IL-6 from the kidney to the plasma and the increased IL-6 plasma levels would thus indeed be secondary events.

Document D28 tested the administration of recombinant IL-6 and the administration of a rat anti-IL-6 antibody to (NZBxNZW)F1 mice. While the administration of recombinant IL-6 exacerbated the development of glomerulonephritis in this mice model, the rat anti-

IL-6 antibody could not prevent glomerulonephritis, also evidenced by the lack of effect on proteinuria. The results in document D28 were however similar for mice that received a rat anti-IL-6 antibody without prior tolerisation in document D13 (see Figure 4). Again therefore the skilled person would have understood that administration of a (rat) IL-6 blocking antibody could reduce the renal manifestation of SLE, lupus nephritis, if and only if the mouse immune response was blocked.

Document A9 studied the relationship between acute-phase responses (C-reactive protein [CRP], di-antitrypsin and α_1-acid glycoprotein), disease course and serum levels of IL-6 during flare-ups in 12 SLE patients. Except in a minority of patients, no relationship between serum IL-6, disease course or symptoms was found. Document A10 studied plasma IL-6 levels in patients with reactive arthritis (ReA), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Plasma levels in SLE patients were not increased. Similar to the situation with the disclosure in document D27, the dilution of IL-6 from the kidney to the plasma and the increased IL-6 plasma levels in some of the patients observed in document A9 were known in the art to possibly be a secondary event. Furthermore, in documents A9 and A10 SLE patients were studied with various clinical manifestations, but both documents were silent on the role of IL-6 in causing the specific renal SLE manifestation, i.e. excretion of urinary protein. Therefore, the skilled person would not have concluded from these disclosures that modulation of the IL-6 signalling is unable to reduce the excretion of urinary protein in SLE.

The appellant had submitted that since administration of IL-6 antibody to mice (see documents A11, A13 and D29) or RA patients (see document A12) increased serum levels of IL-6, this disqualified anti-IL-6R antibody (e.g. as disclosed in document D2) as a suitable alternative for the antibody in document D13. None of these documents however related to SLE. Furthermore, when starting from the teaching in document D13 and knowing from document D2 that anti-IL-6R antibodies too could be used to block IL-6 biological activity and that this led to no increased serum IL-6 concentrations (see document D2, page 8, lines 3-5 and page 10, lines 33-34), the skilled person would not have refrained from using an anti-IL-6R antibody to reduce the excretion of urinary protein.

The results obtained from the experimental model used in the patent could not be compared directly with the results obtained with the model used in document D13 and were therefore not useful for demonstrating a **more potent effect** for anti-IL-6R antibody over the anti-IL-6 antibody in the treatment of SLE as alleged by the appellant, *i.e.* improved survival rates, reduction of serum immunoglobulins, suppression of serum levels of IL-6 in treated mice and the decrease in proteinuria compared to control mice. Before a comparison could be made between models used in different studies (patent and here document D13), the results should be looked at in their totality (including control treatments) rather than with a limited focus on the specific treatment groups and possible difference between them. The model used in document D13 was much more accurate and, as such, clearly different from the mice model used in the patent. This could be deduced e.g. from the responses obtained in the control groups. Whereas document D13 disclosed that 80% of the PBS treated mice showed

proteinuria already after 39 weeks, this value of 80% was reached only after 48 weeks in the model of the patent. Similarly, in document D13 90% of the GL113 treated mice showed proteinuria already after 38 weeks, whereas this value for KH-5 treated mice with proteinuria was reached in the patent only after more than 60 weeks.

Furthermore, a statistical comparison of the results and data on proteinuria presented in the patent and in document D13 (*i.e.* the percentage of mice with proteinuria >100mg) demonstrated the differences in the models. A Cox proportional hazards model fitted to the proteinuria data related to the treatment differences showed a treatment effect which represented the main differences in outcome between vehicle (PBS and saline), control antibody (GL113 and KH-5) and treatment (anti-IL-6 and anti-IL6R) ($p=0.003$). The proteinuria data were also significantly different between the disclosures ($p=0.0001$), and this applied to all treatment groups (*i.e.* also to the PBS/saline group and the control antibody group). An interaction between the two factors was found to be insignificant ($p=0.3305$), which meant that the differences observed between the disclosures could be assumed to be the same for all treatment groups. Accordingly, the IL-6R treated mice in the patent showed an improved proteinuria profile over the IL-6 treated mice in document D13 because the control mice in the patent also showed an improved proteinuria profile over the control mice in document D13. This could indeed also be observed from the data (on proteinuria) presented in the patent and in document D13. Whereas in the patent, in the control group (saline), the percentage of mice with proteinuria only started to increase at the age of about 32 weeks, in document D13, in the control group

(PBS), the percentage of mice with proteinuria started to increase already at the age of 5 months (22 weeks).

It was thus not possible to identify more potent effects for anti-IL-6R antibodies than for anti-IL-6 antibodies in the treatment of SLE.

X. The appellant requested in writing that the decision under appeal be set aside and that the patent be maintained as granted.

The respondent requested in writing that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. Oral proceedings were held in the absence of the duly summoned parties in accordance with Rule 115(2) EPC and Article 15(3) RPBA

Claim 1 - inventive step (Article 56 EPC)

The invention as claimed

3. Claim 1 (see section I) is for the use of an antibody against the interleukin 6 receptor (IL-6R) which neutralises the biological activity of interleukin-6 (IL-6), in the manufacture of a medicament for reducing the excretion of urinary protein in systemic lupus erythematosus (SLE).

4. The invention is based on the observation that the administration of an anti-IL-6R antibody (*i.e.* MR16-1) to NZB/WF1 mice leads to suppression of the excretion

of urinary protein in these mice (see e.g. paragraph [0115] and example 1 of the patent).

5. NZB/WF1 mice (or NZB/NZW F_1 mice) are a known and accepted mouse model that best manifests the pathology of human SLE (see e.g. paragraphs [0009] and [0112] of the patent). The autoimmune nephritis spontaneously occurring in females of these mice includes mesangioproliferative glomerulonephritis and is used as a paradigm for lupus glomerulonephritis in humans (see document D28, page 927, right-hand column, first sentence and page 932, right-hand column, lines 12 to 15, Table 2). Untreated mice show a progressive increase in urinary protein excretion (see document D28, page 929, right-hand column, last sentence).

Closest prior art

6. The board can concur with the opposition division and the respondent that the disclosure in document D13 represents the closest prior art for the purpose of applying the "problem-and-solution" approach to assess whether or not a claimed invention meets the requirements of Article 56 EPC. The appellant has not argued otherwise.

7. Document D13 is entitled "*Interleukin 6 Promotes Murine Lupus in NZB/NZW F_1 Mice*", and its authors investigated the role of IL-6 in SLE by selectively inhibiting IL-6 activity in NZB/WF1 mice, *i.e.* the same mouse model as used in the experiments of the patent in suit known to develop mesangioproliferative glomerulonephritis (see points 4 and 5), by administration of a rat monoclonal antibody (mAb) to mouse IL-6 (see Abstract, lines 1 to 4). Document D13 discloses that, throughout a period of six months, in which the mice were made tolerant to rat

mAb by administration of anti-CD4 antibodies, "*treatment with anti-IL-6 prevented production of anti-dsDNA, significantly reduced proteinuria, and prolonged life*" (see abstract lines 12 to 16, emphasis added by the board). The indicated significant reduction of proteinuria and the prolonged life are illustrated in Figures 4 and 5 of document D13, respectively.

The problem to be solved

8. The technical difference between the teaching in document D13 and the subject-matter of claim 1 is that, instead of an antibody to IL-6 in the prior art, an antibody to the binding partner of IL-6, *i.e.* IL-6R, is administered to the NZB/WF1 mice model of human SLE.

9. In terms of binding, the use of a monoclonal antibody to IL-6 itself or to the IL-6 receptor both lead to the prevention of the binding of IL-6 to its receptor. Moreover, the technical effect of the use of the different antibodies in the mouse model is the same, namely the reduction in proteinuria, *i.e.* the declared reduction of the excretion of urinary protein, in the SLE model developed by these mice.

10. The board therefore considers the problem to be solved to be the provision of an alternative agent for blocking IL-6 signalling and reducing the excretion of urinary protein in SLE.

11. The appellant has argued that the patent demonstrated that anti-IL-6R antibodies had a more potent effect than anti-IL-6 antibodies in the treatment of SLE. This was evidenced by improved survival rates, the reduction of serum immunoglobulins and the suppression of serum

levels of IL-6 in treated mice. Furthermore, it was argued that there was a marked decrease in the occurrence of proteinuria compared to control mice, which was a notable improvement over the findings in document D13.

12. The board however concurs with the respondent that the results obtained with the experimental model in the patent in suit cannot be compared directly with the results obtained with the model used in document D13 and are therefore not useful for demonstrating a more potent effect for the anti-IL-6R antibody over the anti-IL-6 antibody in the treatment of SLE. In fact, statistical analysis by the respondent of the results and data on proteinuria presented in the patent and in document D13 demonstrated differences illustrated e.g. by the fact that, in the control group (saline) in the patent in suit, the percentage of mice with proteinuria started to increase only at the age of about 32 weeks, while in document D13, in the control group (PBS), the percentage of mice with proteinuria started to increase already at the age of five months (22 weeks).

13. The board notes in this context that the appellant has not substantiated during these appeal proceedings that the model of the patent and the model of document D13 are directly interchangeable and that therefore their results are directly comparable. Accordingly, in view of these considerations the board is of the opinion that no case for *improved* effects over the effects in the prior art has been established by the appellant.

Obviousness

14. Document D2 has the title "*Remedy for diseases caused by IL-6 production*" and discloses that the anti-IL-6R antibody MR16-1, *i.e.* the same mAb as used in example 1 of the patent in suit (see also point 4 above), can suppress **mesangium proliferative nephritis** in mice comprising a transgene for IL-6 (IL-6 Tgm; see page 10, lines 50 to 56, and claim 9). Furthermore, Figure 2 demonstrates that administration of mAb MR16-1 to these transgenic mice suppressed the appearance of urinary protein in them (see page 6, lines 48 to 51).

15. The board notes therefore that document D2 teaches the skilled person that administration of the rat mAb MR16-1 results in the reduction of proteinuria in a mice model system known to develop mesangium proliferative nephritis.

16. The board therefore considers that the skilled person, when looking for a solution to the objective technical problem, would, in a obvious manner, consider that the suitability of the rat mAb MR16-1, *i.e.* an anti-interleukin-6 (IL-6) receptor antibody that neutralises the biological activity of IL-6, also makes this antibody suitable for reducing the excretion of urinary protein in the SLE model.

17. Accordingly, the board concludes that the subject-matter of claim 1 was rendered obvious to the skilled person when starting from the disclosure in document D13 in combination with the teaching of document D2.

18. The appellant has submitted that document D10 taught away from the claimed invention because it disclosed that a *rat* anti-IL-6R antibody was not able to reduce the excretion of urinary protein in mice belonging to a different SLE model (page 60, left-hand column, "DISCUSSION"). Attempting to explain this lack of effect - as the respondent does - by referring to the fact that the treated mice were not tolerised prior to administration of the rat mAb amounted to speculation, given that the skilled person knew from document A15 that in NZB/W F1 mice treatment with a *rat* anti-IFN-γ receptor antibody inhibited the onset of glomerulonephritis and the development of proteinuria (see Table 1), despite the mice not being tolerised to the rat antibody.

19. The board considers that the skilled person, contemplating solving the objective technical problem as claimed by combining the teachings of documents D13 and D2 (see point 14), would rather than interpreting the consideration in document D10 that it was "*difficult to determine whether more favourable effects would have resulted if neutralizing antibodies ... failed to occur*" (sentence bridging pages 60 and 61) as teaching away from using rat anti-IL-6R antibody in a tolerised mice SLE model have interpreted this consideration as a well-reasoned possible explanation of the observed effect, even when read in conjunction with the disclosure in document A15. Indeed, a prejudice established in the art against the claimed invention cannot be derived from the disclosure in document D1 or document A15, the latter in fact relating to a totally different mechanism of action, and this has not been argued by the appellant either.

20. The appellant has argued that the prior art, such as the disclosures in documents D27 and D28 and A9 and A10, cast doubt on whether an agent which disrupted the IL-6 pathway could provide a useful therapy for SLE. Therefore, the skilled person would not have considered that modulation of the IL-6 pathway, in particular by using an anti-IL-6 receptor antibody, was a suitable alternative to the use of anti-IL-6 antibody as taught in document D13 for reducing the excretion of urinary protein in SLE.

21. Similarly to document D10, the board notes in this respect that the appellant, on the basis of these four disclosures in the prior art, has not argued that they establish a prejudice against the usefulness of an anti-IL-6R antibody in solving the objective technical problem, let alone that they would restrain the skilled person from solving it as claimed.

22. A final argument of the appellant was based on the fact that documents A11 to A13 and D29 demonstrated that treatment of mice with anti-IL-6 antibody was associated with markedly increased serum levels of IL-6. Thus, the administration of a neutralising anti-IL-6 antibody to mouse was expected to increase the biological activity of IL-6 *in vivo*.

23. The board in this respect agrees with the respondent that none of the documents referred to in fact relates to SLE. Furthermore, when starting from the teaching in document D13 the skilled person would already start from knowledge of the usefulness of anti-IL-6 for reducing proteinuria in SLE. Furthermore, from document D2 the skilled person knew both that anti-IL-6R antibodies can block IL-6 biological activity and that this does not lead to increased serum IL-6

concentrations (see document D2, page 8, lines 3 to 5 and page 10, lines 33 to 34). Accordingly, the disclosures in documents A11 to A13 and D29 cannot deter the skilled person from using of an anti-IL-6R antibody to reduce the excretion of urinary protein either.

24. In view of the above considerations the board concludes that the skilled person would have solved the objective technical problem formulated in point 10 above in an obvious manner and would have arrived at the claimed subject-matter by combining of the disclosure in document D13 with that in document D2. Other disclosures in the prior art would not have discouraged him from doing so.

25. The subject-matter of claim 1 therefore lacks inventive step. Accordingly, as decided by the opposition division, the patent does not comply with the requirements of the EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated