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Datasheet for the decision of 9 September 2014

Case Number: T 2392/09 - 3.3.04

Application Number: 98931006.5

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Title of invention:
Chimeric interleukin-6 soluble receptor/ligand protein, analogs thereof and uses thereof

Patent Proprietor:
Yeda Research and Development Co., Ltd.

Opponent:
Zwicker, Jörk

Headword:
Chimeric protein/YEDA RESEARCH

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

Keyword:
"Main request, claim 1 - Added matter (no), Novelty (no)"
"Auxiliary request I -
Added matter (no), novelty (yes), inventive step (yes)"

Decisions cited:
T 0165/00, T 1462/08

Catchword:

-

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Case Number: T 2392/09 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 9 September 2014

Appellant: (Patent Proprietor)	Yeda Research and Development Co., Ltd. The Weizmann Institute of Science P.O. Box 95 76100 Rehovot (IL)
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Representative:	Zwicker, Jörk ZSP Patentanwälte Partnerschaftsgesellschaft Radlkoferstrasse 2 81373 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 5 October 2009 concerning maintenance of the European Patent No. 0991661 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Claes
	M. Blasi

Summary of Facts and Submissions

I. European patent No. 0 991 661 with the title "*Chimeric interleukin-6 soluble receptor/ligand protein, analogs thereof and uses thereof*" was granted on the basis of the European patent application No. 98931006.5, filed as international application PCT/IL98/000321 and published as WO 99/002552.

II. Claims 1 to 5 of the application as filed read:

"1. A chimeric glycosylated soluble interleukin-6 receptor (sIL-6R)-interleukin-6 (IL-6) protein (sIL-6R/IL-6) and biologically active analogs thereof, comprising a fusion protein product between essentially all of the naturally occurring form of sIL-6R and essentially all of the naturally occurring form of IL-6, said sIL-6R/IL-6 and analogs thereof being glycosylated in a similar fashion to the glycosylation of naturally occurring sIL-6R and IL-6.

2. A chimeric sIL-6R/IL-6 protein and biologically active analogs thereof according to claim 1, wherein said sIL-6R is fused to IL-6 via a peptide linker molecule.

3. A chimeric sIL-6R/IL-6 protein and biologically active analogs thereof according to claim 2, wherein said linker is a very short, non-immunogenic linker of about 3 amino acid residues.

4. A chimeric sIL-6R/IL-6 protein and biologically active analogs thereof according to claim 3, wherein said linker is a tripeptide of the sequence E-F-M (Glu-Phe-Met).

5. A chimeric sIL-6R/IL-6 protein and biologically active analogs thereof according to claim 2, wherein said linker is a peptide of 13 amino acid residues of the sequence E-F-G-A-G-L-V-L-G-G-Q-F-M (Glu-Phe-Gly-Ala-Gly-Leu-Val-Leu-Gly-Gly-Gln-Phe-Met)."

III. The appeals from the patentee (hereinafter "appellant I") and from the opponent (hereinafter "appellant II") stem from the interlocutory decision of the opposition division that the patent could be maintained in amended form on the basis of an auxiliary request I filed during the oral proceedings before them. The grounds for opposition invoked were under Article 100(a) EPC (in conjunction with Articles 54 and 56 EPC) and Article 100(c) EPC. The opposition division found the main request before them (claims as granted) to comply with the requirements of Article 123(2) EPC (ground under Article 100(c) EPC), but the subject-matter of claim 1 of this request to lack novelty under Article 54(1),(3) EPC.

IV. Claim 1 of the patent read:

"1. A chimeric glycosylated soluble interleukin-6 receptor (sIL-6R)-interleukin-6 (IL-6) protein (sIL-6R/IL-6) and biologically active analogs thereof comprising a fusion protein product between sIL-6R and IL-6, said sIL-6R/IL-6 and said analogs thereof retaining the same glycosylation pattern as the naturally occurring sequences when expressed in mammalian cells, wherein sIL-6R and IL-6 are the naturally occurring forms or are characterized by amino acid additions up to 20 amino acids, deletions up to 30 amino acids and/or substitutions up to 30 amino acids to the naturally occurring sequences and wherein said sIL-6R is fused to IL-6 directly or via a peptide

linker molecule which is a tripeptide of the sequence E-F-M (Glu-Phe-Met), or a peptide of 13 amino acid residues of the sequence E-F-G-A-G-L-V-L-G-G-Q-F-M (Glu-Phe-Gly-Ala-Gly-Leu-Val-Leu-Gly-Gly-Gln-Phe-Met)." (emphasis added by the board)

Claims 1, 4-13, 17 and 18 of auxiliary request I read:

"1. A chimeric glycosylated soluble interleukin-6 receptor (sIL-6R)-interleukin-6 (IL-6) protein (sIL-6R/IL-6) and biologically active analogs thereof comprising a fusion protein product between sIL-6R and IL-6, said sIL-6R/IL-6 and said analogs thereof retaining the same glycosylation pattern as the naturally occurring sequences when expressed in mammalian cells, wherein
(a) sIL-6R and IL-6 are the naturally occurring forms or are **characterized by** amino acid additions up to 20 amino acids, deletions up to 30 amino acids or substitutions up to 30 amino acids to the naturally occurring sequences and wherein said sIL-6R is fused to IL-6 directly; or
(b) sIL-6R and IL-6 are the naturally occurring forms or are **characterized by** amino acid additions up to 20 amino acids, deletions up to 30 amino acids and/or substitutions up to 30 amino acids to the naturally occurring sequences and wherein said sIL-6R is fused to IL-6 via a peptide linker molecule which is a tripeptide of the sequence E-F-M (Glu-Phe-Met), or a peptide of 13 amino acid residues of the sequence E-F-G-A-G-L-V-L-G-G-Q-F-M (Glu-Phe-Gly-Ala-Gly-Leu-Val-Leu-Gly-Gly-Gln-Phe-Met).

4. The chimeric sIL-6R/IL-6 protein according to any one of claims 1 to 3, wherein said protein is produced in vitro in mammalian cells in a fully processed form.

5. The chimeric sIL-6R/IL-6 protein according to claim 4, wherein said protein is produced in human cells.

6. The chimeric sIL-6R/IL-6 protein and biologically active analogs thereof according to any one of claims 1 to 5, wherein said chimeric protein and analogs are characterized by being capable of inhibiting the growth of highly malignant cancer cells, eliciting the in vivo engraftment of human hematopoietic cells in bone marrow transplantations or of protecting liver from hepatotoxic agents.

7. The chimeric slL-6R/IL-6 protein and biologically active analogs thereof according to claim 6, wherein said malignant cancer cells are malignant melanoma cells.

8. A DNA sequence encoding a chimeric sIL-6R/IL-6 protein and biologically active analogs thereof according to any one of claims 1 to 5.

9. A DNA vector comprising the DNA sequence according to claim 8, said vector being suitable for expression of said chimeric protein in mammalian cells.

10. The DNA vector according to claim 9, wherein said vector is suitable for expression of said chimeric protein in human cells.

11. The DNA vector according to claim 9 or 10, wherein when said vector is expressed in said cells, the expressed chimeric protein has a sequence that permits full processing of the chimeric protein by said cells and secretion of the fully processed chimeric protein

from the cells into the culture medium in which said cells are grown.

12. Transformed mammalian cells containing the DNA vector according to any one of claims 9 to 11 which are capable of expressing the sIL-6R/IL-6 chimeric protein sequence carried by said vector and of fully processing the expressed protein and secreting it into the culture medium in which said cells are grown.

13. A method for producing a chimeric protein or biologically active analogs thereof according to any one of claims 1 to 7, comprising growing transformed cells according to claim 12 under conditions suitable for expression, processing and secretion of said protein or analogs into the culture medium in which said cells are grown; and purifying said protein or analogs from said culture medium.

15. Use of the chimeric sIL-6R/IL-6 protein or analogs according to any one of claims 1 to 5, salts of any one thereof, and mixtures thereof, as an inhibitor of cancer cell ex vivo.

17. A pharmaceutical composition comprising as active ingredient the chimeric sIL-6R/IL-6 protein or analog thereof according to any one of claims 1 to 5, salts of any one thereof and mixtures thereof, or the DNA sequence according to claim 8 and a pharmaceutically acceptable carrier, diluent or excipient.

18. Use of the chimeric sIL-6R/IL-6 protein or analog thereof according to any one of claims 1 to 5, salts of any one thereof and mixtures thereof, or the DNA sequence according to claim 8 for the preparation of a pharmaceutical composition for treating mammalian

cancers by way of inhibition of mammalian cancer cells, for enhancement of bone marrow transplantation by way of eliciting engraftment of human hematopoietic cells in bone marrow transplantation, for increasing hematopoeisis, for treating liver or neurological disorders, or for other applications in which IL-6 or sIL-6R are used." (emphasis added by the board)

Claims 2 and 3 were directly dependent on claim 1. Claims 14, 16 and 19 were directly dependent on claims 13, 15 and 18 respectively.

V. The following documents are referred to in the present decision:

D1: Fischer *et al*. (1997), Nature Biotechnology, Vol. 15, pages 142-145.

D5: Mackiewicz *et al*. (1995), Annals of the New York Academy of Sciences, Vol. 762, pages 361-374.

D9: WO97/32891

D20: Vollmer *et al*. (1996), J. Immunological Methods, Vol. 99, pages 47-54.

D22: Yawata *et al*. (1993), EMBO J., Vol. 12(4), pages 1705-1712.

D25: Borys *et al*. (1993), BIO/TECHNOLOGY, Vol. 11, pages 720-724.

D26: Rose-John & Heinrich (1994), Biochem. J., Vol. 300, pages 281-290.

D27: Walev *et al*. (1996), Proc. Natl. Acad. Sci. USA,

Vol. 93, pages 7882-7887.

D28: Vollmer *et al.* (1996), Infection and Immunity, Vol. 64(9), pages 3646-3651.

D29: Matthews *et al.* (2003), J. Biol. Chem., Vol. 278(40), pages 38829-28839.

D30: Xue *et al.* (2004), Nucl. Acid. Res., Vol. 32, Web Server issue, W562-W565 *(DOI: 10.1093/nar/gkh422).*

VI. Appellant I submitted in its statement of grounds of appeal arguments in favour of the novelty of the subject-matter of claim 1 of the main request (claims as granted) over the disclosure in document (D9) and submitted a further document.

VII. Appellant II submitted with its statement of grounds of appeal arguments against the compliance of the claims with the requirements of Article 123(2) EPC, against the novelty of the subject-matter of claims 1, 4 to 13 and 18 and against the fact that the subject-matter of the claims involved an inventive step. In relation to some issues appellant II referred to its submissions of the opposition proceedings. In addition appellant II submitted three further documents.

VIII. Appellant I filed a reply to appellant II's statement of grounds of appeal.

IX. After having been summoned to oral proceedings both appellants announced in letters of 24 July 2014 and 26 August 2014 respectively, that they would not attend the oral proceedings.

X. Oral proceedings took place as summoned on 9 September 2014 in the absence of the parties.

XI. The arguments of appellant I can be summarised as follows:

Main request - claim 1

Added matter

The passage on page 20, lines 11 to 19, of the application as filed did not only refer to "conservative" substitutions, but to substitutions in general, and the wording "the above-defined sequences" in the passage not only referred to the preferred substitutions on page 20, lines 5 and 6 (i.e. conservative substitutions), but also the substitutions as disclosed e.g. on page 19, lines 3 to 6 and in the paragraph bridging pages 19 and 20. The application as filed therefore provided a basis for the "and/or" connector in claim 1.

The omission of "essentially" from the expression "essentially the same glycosylation pattern" of the feature disclosed on page 7, lines 3 to 8 of the application as filed did not result in added matter, but was similar to deleting "about" or "approximately" from a claim in order to fulfil the requirements of Article 84 EPC, without thereby being contrary to the requirements of Article 123(2) EPC even if the specification always used the phrases. Therefore, "essentially the same glycosylation pattern" comprised two alternatives, i.e. first 100% identical to the natural glycosylation pattern, and, second, allowing some minor deviations compared to the natural glycosylation pattern and the amendment merely removed

one of these alternatives. Also, additional passages in the application as filed gave support for the feature "retaining the same glycosylation pattern" such as e.g. on page 3, lines 6 to 10 and on page 17, lines 1 to 11.

Novelty

The analogs of claim 1 differed from the constructs as disclosed in document (D9) by three parameters: i) the absence of a linker; ii) the natural glycosylation pattern; and iii) their particular biological activity.

The wording "directly fused" in claim 1 excluded the presence of linkers such as comprised in the constructs disclosed in document (D9). One and the same amino acid sequence could not be a linker and at the same time be considered as part of a modified sIL-6R. A "linker" connecting two parts of a fusion protein had a particular biological function and thus required a particular amino acid sequence (see e.g document (D30), page W562, right-hand column, first full paragraph), such as e.g. the sequences of the linkers of document (D9).

The fusion protein of the patent in suit (which had an overall length of about 532 amino acids), had a molecular weight of 57 kD when expressed in yeast cells (see page 3, lines 44 to 46 of the patent in suit) and a molecular weight of 85 kD when expressed in mammalian cells (HEK or CHO cells). The latter was expected for a fusion protein containing essentially all of the natural sIL-6R and IL-6 amino acid residues and being fully glycosylated. The fusion proteins disclosed in document (D9) had a molecular weight in the range of 70 to 75 kD when expressed in mammalian COS-7 cells (see document (D9) page 8, line 15). The fusion proteins

disclosed in document (D9) were about 4% shorter than the fusion protein of the patent in suit. A skilled person would thus expect a molecular weight in the range of about 81.6 kD rather than 70 to 75 kD when fully glycosylated in mammalian cells, unless the domain lacking in the fusion proteins of document (D9) would e.g. be peppered with numerous glycosylation sites, which was not the case. The C-terminal region of the fusion proteins of the patent in suit having Val-356 as the C-terminus contained a motif for N-glycosylation, which would be deleted when at least 12 amino acids were deleted from this C-terminus as was required to have claim 1 to read on the constructs of document (D9). Their glycosylation pattern had therefore to be different.

Moreover, document (D25) disclosed that culture conditions could effect the glycosylation of recombinantly expressed proteins. Therefore, whereas the patent in suit disclosed how to obtain properly glycosylated proteins (e.g. paragraph [0064]), document (D9) was not enabling for such conditions.

Accordingly, the particular fusion proteins of document (D9) obtained after the expression in COS-7 cells were not properly glycosylated and did not "retain the same glycosylation pattern as the naturally occurring sequences when expressed in mammalian cells" as required by claim 1.

The biological activity of the compounds of claim 1 was described in paragraphs [0031] and [0032] of the patent in suit (in particular growth arrest of highly malignant mammalian cells such as F10.9 melanoma cells) and evidence for such activity was provided in example 3. However, document (D9) was silent on such

biological activity of the disclosed fusion proteins and appellant II had not provided any evidence for such biological activity.

Auxiliary request I

Novelty

Claim 1

"[N]aturally occurring sequences of sIL-6R" were defined in the patent in suit as "*natural products of the human body found as glycoproteins in blood and in urine*" (see paragraph [0002]. There was, furthermore, a clear and unambiguous definition of the C-terminus of the "naturally occurring sequences of sIL-6R" in the description of the patent in suit, i.e. Val-356 (see patent in suit page 4, line 52 to page 5, line 2; page 6, lines 25 to 28; page 8, lines 1 to 5 and example 1).

Artificially produced forms of sIL-6R, e.g. by *in vitro* treatment with toxins or bacterial metallo-proteinases, were not "naturally occurring sequences" as referred to in claim 1. Documents (D27) to (D29) were not supportive regarding the natural C-terminus of sIL-6R since (a) they merely related to *in vitro* studies on "shedding", *i.e.* proteolytic cleavage, using non-natural conditions or enzymes and did not determine the exact cleavage site. In particular, document (D27) reported on shedding of IL-6R induced by pore-forming toxins. This was exceptional and not natural so that the cleavage products generated could not be regarded as "natural products found in the human body". Moreover, the authors did not determine the exact position of the cleavage site(s). Document (D28) described the shedding of IL-6R by bacterial metallo-

proteinase and it was hypothesised that these proteinases might mimic the action of the end shedding protease (generating the "natural products of IL-6R"). The exact cleavage site could not be determined (page 3650, right-hand column, first full paragraph) and the cleavage did not reflect the natural situation (see document (D28), abstract lines 15 and 16 and page 3649, right-hand column, lines 8 to 15). Document (D29) found that low cholesterol levels might play a role in shedding of membrane-bound IL-6R and thereby in the immuno-pathogenesis of human diseases. However, the cleavage site was not determined. Furthermore, it was not stated in document (D20) that the C-terminus of the shedded form of sIL-6R is amino acid 336 as contended by appellant II. It was clear from the legend of Figure 1 that the DNA having aa336 as the C-terminus was merely one of the artificial constructs used for expression in the yeast *Pichia pastoris* and the authors had no idea about the natural cleavage site (page 53, left-hand column, ultimate paragraph).

There was accordingly no room for interpreting the C-terminal amino acid of naturally occurring sIL-6R to be different than Val-356. In order for claim 1 to read on the fusions disclosed in document (D9) therefore it required a deletion of 33 amino acids, which was not within the scope of claim 1 of the auxiliary request. The subject-matter of claim 1 was therefore novel over the disclosure in document (D9).

Claims 4-13, 17 and 18

No arguments were presented by appellant I.

Inventive step

Claim 1

Based on the teaching of document (D1) the skilled person would not have modified the sIL-6R/IL-6 fusion protein disclosed therein in such a way as to obtain fusion proteins falling within the scope of claim 1.

Document (D1) disclosed that "*To keep the overall size of the fusion protein as small as possible we excluded the N-terminal Ig domain as well as the C-terminal tether domain of the human sIL-6R, which had previously been shown not to contribute to ligand binding and biological activity of the IL-6R protein*" (see page 143, left-hand column, first paragraph). This statement in document (D1) applied in general to all expression systems and was not, as alleged by appellant II, restricted to yeast expression systems for producing the fusions. In fact, the authors of document (D1) deleted the Ig-domain since they (mistakenly) believed that it did not have any biological function. Further documents corroborated this finding, such as document (D20) (see page 53, 1st column, 2nd paragraph of the section "Discussion") and document (D22) (see paragraph bridging pages 1709 and 1710). There existed a strong prejudice against the use of a sIL-6R/IL-6 fusion protein containing the Ig-like domain for therapeutic uses. Accordingly, document (D1) taught away from the now-claimed larger fusions, irrespective of the mode of their expression.

The statement in the patent in suit in paragraph [0005] ("*it is important to remain as close as possible to the natural forms of the protein*") did not relate to the primary amino acid sequence but to glycosylation and

was in the context of avoiding the undesirable generation of e.g. antibodies due to improper glycosylation.

Claims 2 to 19

Document (D5) could only be of relevance for questioning inventive step of the subject-matter of claims 15, 16, 18 and 19.

Claims 2 to 19 all included back-references to claim 1 and their subject-matter was therefore likewise inventive.

Claim 18

Even if the disclosure of document (D9) were to constitute prior art pursuant to Article 54(2) EPC, it would not render the subject-matter of claim 18 to lack inventive step.

The fusion protein disclosed in document (D9) was not within the scope of claim 1. Furthermore, from the stimulation of haptoglobin expression a skilled person would not have concluded that the fusion protein was useful for the treatment of liver diseases. None of the common liver diseases were characterised by a reduced expression of haptoglobin (which was synthesised in the liver). Actually, a reduced haptoglobin level could be indicative of hemolysis which had nothing to do with a liver dysfunction. An increased haptoglobin level that could be found in various cancers did certainly not call for stimulation of haptoglobin expression.

Accordingly, based on the teaching of document (D9) the skilled person had absolutely no incentive to try to

use the sIL-6R/IL-6 fusion protein for treatment of liver disorders. The subject-matter of claim 18 therefore involved an inventive step also in this aspect.

XII. The arguments of appellant II can be summarised as follows:

Main request

Appellant II's submissions were restricted to its statement of grounds of appeal, which contained mainly arguments on the issues relating to auxiliary request I. Some of these arguments, besides being relevant for this auxiliary request I are also relevant for the claims of the main request. The arguments here, however, are summarised in the context of auxiliary request I.

Auxiliary request I

Added matter - claim 1

The "and/or" connector in part (b) of claim 1 had no basis in the application as filed. The passages on page 20, lines 6 to 14, only referred to "conservative substitutions" but not to substitutions in general. Even when assuming that the passage referred to on page 20 provided an adequate basis for the "and/or" connector, then the text passage only provided a basis for combinations of deletions, additions and/or conservative substitutions. Furthermore, the number of allowable conservative substitutions was not specified in the passage. Claim 1, however, referred specifically to "amino acid additions up to 20 amino acids", "deletions up to 30 amino acids" and/or "substitutions

up to 30 amino acids". None of these numerical parameters had a basis in the passage referred to on page 20 of the application as filed.

"*The objection under Art. 123(2) EPC against the expression 'the same glycosylation pattern' in claim 1 is maintained. In this regard, we refer to our arguments presented in the opposition brief dated July 18, 2007.*"

Novelty

Claim 1

Document (D9), which was comprised in the prior art pursuant to Article 54(3) and (4) EPC, described fusion proteins comprising IL-6 and sIL-6R, in particular amino acids 1-323 of IL-6R and amino acids 29-212 of IL-6 connected to each other via a linker of 18 amino acids or 13 amino acids (see document (D9), Figures 1 and 2 respectively and page 3, lines 15 to 24) which were glycosylated when expressed in mammalian cells (COS-7) (example 3). Claim 1 in the alternative (a) read on the fusions disclosed in document (D9). Accordingly, the subject-matter of alternative (a) of claim 1 was not novel.

Claim 1 allowed for additions up to 20 amino acids, deletions up to 30 amino acids **or** substitutions up to 30 amino acids in either naturally occurring sequences of the sIL-6R part and the IL-6 part of the fusion protein, where said parts are then directly fused to each other.

Any amino acid sequence could arbitrarily be defined as a linker or as part of a modified sIL-6R. Thus, the

linkers present in the fusion proteins disclosed in document (D9) could be part of a modified sIL-6R or part of a modified IL-6 molecule where said parts are then **directly** fused to each other.

There was no controversy that amino acids 29-212 as present in the fusion protein shown in Figure 1 of document (D9) constituted the naturally occurring mature form of IL-6 (see patent in suit, paragraph [0037], lines 7 to 9). In the fusion protein according to Figure 1 and example 3 of document (D9) the IL-6 part was modified by the addition of 18 amino acids of the linker at its N-terminal end, thereby fulfilling the requirements of part (a) of claim 1. The situation was different when interpreting a "naturally occurring sIL-6R", which was not defined in the patent in suit. A skilled person considered this to refer to any sequence of sIL-6R which could be found in nature.

Several soluble forms of IL-6R (sIL-6R) existing in nature lacked the transmembrane region, the cytoplasmic region and had different numbers of amino acids in the extracellular domain. These were formed by alternative splicing or "shedding" (proteolytic cleavage). The alternative splicing variant disclosed in documents (D20) and (D26) contained amino acids 20-355 followed by 10 additional amino acids at the C-terminal end. At least four shedding variants of sIL-6R existed: (i) a shedded form obtainable by induction with phorbol ester, generated by cleavage with ADAM17 (=TACE) comprised amino acids 20-357 (see document (D26)) or amino acids 20-336 (see document (D20); (ii) a shedded form induced by pore-forming toxins with the C-terminus in the region between Asn-337 and Ser-348 (see document (D27); (iii) a shedded form obtainable by cleavage with a metalloproteinase (SMP) from *Serratia marcescens*

having a C-terminus in the region ranging from Ser-320 to Thr-335 (see document (D28); and (iv) a shedded form generated by cleavage with ADAM10, for which the cleavage site was not characterised yet (see document (D29)). Further variants of sIL-6R had been described without indicating by which mechanism they were generated, such as the naturally occurring variant spanning amino acids 20 to 356 as described in the patent in suit. However, none of the cited documents and none of the references cited in the patent in suit disclosed a IL-6R variant having Val-356 as C-terminal end. Accordingly, various forms of sIL-6R which exhibited differences in their C-terminus existed in nature.

In particular, the shedded form of sIL-6R obtained through induction by pore-forming toxins as disclosed in document (D27) had a C-terminus in the region between Asn-337 and Ser-348 of IL-6R. Assuming that Ser-348 constituted the C-terminus of this naturally occurring sequence of sIL-6R, the sIL-6R part of the fusion protein according to Figure 1 of document (D9) differed from this shedded form by the absence of amino acids 324-348, *i.e.* by the deletion of 25 amino acids, whereby part (a) of claim 1 allowed for deletions of up to 30 amino acids in the sIL-6R part. The same conclusion could be reached when starting from a shedded form of sIL-6R disclosed in document (D28). The fusion protein of example 3 of document (D9) thus fulfilled the requirements of part (a) of claim 1.

The molecular weight of the non-glycosylated fusion of document (D9) was expected to be about 56 kDa (see document (D21), second page), whereas the observed molecular weight of the same fusion when expressed in the mammalian cells was 70-75 kDa (see document (D9),

page 8, lines 13 to 21). This confirmed that the two fusion proteins generated in example 3 of document (D9) were glycosylated.

The comparison of the molecular weight of the fusion proteins of document (D9), *i.e.* 70-75 kDa, and of the fusion prepared in example 2 of the patent in suit, having an alleged expected molecular weight of 85 kDa, (as conducted by appellant I) was not meaningful, as the molecular weight of the fusions of document (D9) should be compared to that of the *claimed* fusion proteins. Furthermore, the calculation obtaining a molecular weight of 85 kDa in the patent in suit was flawed. While the molecular weight of the artificial construct sIL-6RδVal might be 60 kDa when isolated from an expression system, it was not the correct molecular weight for naturally occurring sIL-6R isolated from human urine, which fell in a range between 40 and 60 kDa (see document (D17), page 4, lines 27 to 30). Thus, assuming that the information on the size of glycosylated IL-6 in paragraph [0066] of the patent in suit was correct (23-26 kDa), the expected size for a glycosylated fusion protein of sIL-6R and IL-6 was in a range between 63 and 86 kDa. The observed molecular weight of 70-75 kDa of the fusion proteins disclosed in document (D9) fell well into this range. The fusion proteins produced in example 3 of document (D9) were thus "properly glycosylated".

Since the "glycosylation" feature in claim 1 was a "product-by-process" feature, any protein meeting the structural requirements of the claim and expressed in mammalian cells fell by definition within the ambit of the claim. The fusion proteins produced according to example 3 of document (D9) were expressed in mammalian cells, namely COS-7 cells. Thus, said fusion proteins

retained the "same glycosylation pattern as the naturally occurring sequences when expressed in mammalian cell".

Claims 4-3, 17 and 18

"*The novelty objections against the subject-matter of claims 4-13, 17 and 18 are maintained. In this regard, we refer to the explanations and arguments presented in section D.2 of our opposition brief dated July 18, 2007. These novelty objections were not discussed during the oral proceedings held in the opposition proceedings.*"

The "additional features" of claims 4 to 13, 17 and 18 were also disclosed in document (D9) (section D.2 of the notice of opposition).

The features of claims 4 to 6, which were directly or indirectly dependent on claim 1, were disclosed in document (D9). Examples 1 and 2 of document (D9) disclosed two particular expression vectors comprising a DNA sequence encoding a fusion protein of sIL-6R and IL-6. The subject-matter of independent claims 8 and 9 therefore lacked novelty. The additional features of claims 10 and 11, both dependent on claim 9, were also disclosed in document (D9). Example 3 of document (D9) disclosed a method for the expression of the disclosed fusion proteins in COS-7 cells. Accordingly, the subject-matter of independent claims 12 and 13 also lacked novelty. Document (D9) also disclosed the pharmaceutical composition comprising the sIL-6R/IL-6 fusions and their use for increasing hematopoeisis. Therefore, independent claims 17 and 18 lacked novelty.

Inventive step

Claim 1

The sIL-6R/IL-6 fusion protein of claim 1 differed from the sIL-6R/IL-6 fusion protein disclosed in document (D1) in respect of two features: (a) the latter was expressed in yeast cells (which cells did not provide a mammalian glycosylation pattern) and (b) it lacked the Ig-like domain of sIL-6R (see document (D1), Figure 1). The objective problem to be solved was thus the provision of an alternative fusion protein to those disclosed in document (D1). There was no doubt that it was technically feasible for the skilled person to produce such proteins as subject-matter of claim 1.

The statement in document (Dl) (page 143, left-hand column, lines 6 to 9) "*To keep the overall size of the fusion protein as small as possible we excluded the N-terminal Ig domain as well as the C-terminal tether domain of the human sIL-6R*" did not discourage the skilled person from modifying the fusion protein of document (Dl) by re-introducing the Ig-domain or the C-terminal tether domain. In fact, the sentence was framed in the specific context of protein expression in yeast host cells and a skilled person was aware that this did not apply to all expression systems. In particular, in the context of mammalian expression systems, there was no necessity to keep the size of the fusion protein as small as possible. Accordingly, the skilled person would have disregarded the statement when turning to mammalian expression systems.

Furthermore, the patent in suit itself emphasised in the first sentence of [0005], that "*The common experience in developing recombinant proteins which can*

be used for treating human patients has shown that it is important to remain as close as possible to the natural forms of the proteins, as they are found in the human body, in order to avoid triggering of antibodies and other side effects observed with non-natural recombinant products". There existed therefore a motivation (i) to express the fusion protein disclosed in document (Dl) in mammalian cells (as opposed to yeast cells) to obtain the natural glycosylation pattern; and (ii) to include the Ig-like domain into the sIL-6R part of the molecule so that all parts naturally present in the individual proteins are also present in the combined fusion protein. Accordingly, the skilled person would have modified the fusion protein disclosed in document (Dl) in an obvious manner and arrived at a fusion protein falling within the ambit of claim 1.

Claims 2 to 19

"The subject-matter of the remaining claims 2-19 does not involve an inventive step over D1 in view of the common knowledge of the skilled person or in view of the disclosure of D5. For detailed explanations and arguments we refer to section E.3 of our opposition brief dated July 18, 2007. These inventiveness objections were not discussed during the oral proceedings held in the opposition proceedings."

The subject-matter of claims 2 to 14 lacked an inventive step mainly in view of the disclosure in document (D1) and the common knowledge of the skilled person.

Document (D5) disclosed that IL-6 and sIL-6R could be used in the treatment of melanoma. Therefore the

subject-matter of claims 15 and 16 where not inventive in view of the disclosure of document (D1) read in the light of document (D5).

The subject-matter of claims 17, 18 and 19 was not inventive in view of the disclosure in document (D1) taken on its own, in view of the common knowledge of the skilled person or in view of the disclosure in document (D5) respectively.

Claim 18

Claim 18 concerned the use of the fusion proteins of the invention for the preparation of a pharmaceutical composition for treating *inter alia* liver disorders. The relevant date for this aspect of the claimed subject-matter was the filing date of 9 July 1998. Document (D9) was thus prior art pursuant to Article 54(2) EPC. Document (D9) disclosed the fusion proteins of claim 1 and further that such fusion proteins, upon administration, have medical applications. Example 4 (page 8, line 28 to page 10, line 12) demonstrated that the fusion proteins described were capable of inducing haptoglobin expression and secretion in hepatoma cell lines and hence that liver cells were a potential target for fusion proteins comprising sIL-6R and IL-6. Based on this information it was obvious to the skilled person to use the fusion proteins for the treatment of haptoglobin-deficiency or other liver disorders. Consequently, the subject-matter of claim 18 did not involve an inventive step over the disclosure in document (D9).

XIII. The parties' requests in the written proceedings were:

Appellant I requested as its main request that the decision under appeal be set aside and that the patent be maintained as granted, and, as an auxiliary request, that the appeal of appellant II be dismissed, i.e. that the patent be maintained on the basis of the auxiliary request I as considered allowable by the opposition division.

Appellant II requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1. The appeals are admissible.

2. The duly summoned appellants did not attend the oral proceedings as announced in their letters of 24 July 2014 and 26 August 2014 respectively. In accordance with Rule 115(2) EPC and Article 15(3) RPBA, the board decided to continue the proceedings, taking into account the principle of procedural economy, and the parties were treated as relying on their written case.

Main request - claim 1

Added matter

3. In the context of the ground for opposition pursuant to Article 100(c) EPC, the opposition division found claim 1, and also claim 1 of auxiliary request I, to comply with the requirements of Article 123(2) EPC. Upon appeal, appellant II has anew argued that claim 1 infringed the requirements of Article 123(2) EPC. These

arguments apply to claim 1 of both the main request and auxiliary request I.

4. Appellant II held that the "and/or" connector in the wording "sIL-6R and IL-6 are the naturally occurring forms or are characterized by amino acid additions up to 20 amino acids, deletions up to 30 amino acids and/or substitutions up to 30 amino acids to the naturally occurring sequences" lacked a basis in the application as filed. It was furthermore submitted that the expression "*the same glycosylation pattern*" in claim 1 constituted added matter.

5. The board is satisfied that a general basis for the wording of claim 1 can be found in the wording of claims 1 to 5 as filed (see section II). It therefore needs to be assessed whether the amendments contested by appellant II comply with the requirements of Article 100(c)/123(2) EPC.

"And/or" connector

6. For assessing whether the "and/or" connector in the wording "sIL-6R and IL-6 are the naturally occurring forms or are characterized by amino acid additions up to 20 amino acids, deletions up to 30 amino acids and/or substitutions up to 30 amino acids to the naturally occurring sequences" finds a basis in the application as filed the following passages in the application as filed are of relevance:

6.1 On page 6, line 20 to page 7, line 8 of the application as filed it is stated: "*... these analogs being sIL-6R/IL-6 chimeras in which one or more amino acid residues have been deleted, added or substituted by others, the only limitation on such analogs being that they retain*

most of the naturally occurring sIL-6R and IL-6 sequence. For example, amino acid additions to the naturally occurring sIL-6R and IL-6 sequences are preferably limited to up to between about 20 amino acids, and preferably these additions are at the site of junction between the sIL-6R and IL-6, i.e. the linker molecule. Likewise, deletions from the sIL-6R and IL-6 sequences are preferably limited to up to between about 20-30 amino acids; and substitutions of amino acid residues in the sIL-6R and IL-6 sequences by other amino acid residues are preferably also limited to up to between about 20-30 amino acids. All of the aforesaid deletions, additions and substitutions are acceptable in accordance with the present invention when the so-modified analogs that are obtained retain essentially the biological activity of the sIL-6R/IL-6 chimera composed of essentially the naturally-occurring sequences, and retain essentially the same glycosylation pattern of the chimera composed of essentially the naturally-occurring sequences when expressed in mammalian cells." (emphasis added by the board)

6.2 On page 18, lines 4 to 11 of the application as filed it is stated: "*The present invention also concerns analogs of the above chimeric sIL-6/IL-6 protein of the invention, which analogs retain essentially the same biological activity of the chimeric protein having essentially only the naturally occurring sequences of slL-6R and IL-6. Such analogs may be ones in which up to about 30 amino acid residues may be deleted, added or substituted by others in the sIL-6R and/or IL-6 moieties of the chimeric protein, such that modifications of this kind do not substantially change the biological activity of the chimeric protein analog*

with respect to the chimeric protein itself ..." (emphasis added by the board)

6.3 On page 20, lines 5 to 19 of the application as filed it is stated: "*Preferred changes for analogs in accordance with the present invention are what are known as 'conservative' substitutions. Conservative amino acid substitutions of those in the chimeric protein having essentially the naturally-occurring sIL-6R and IL-6 sequences, may include synonymous amino acids within a group which have sufficiently similar physicochemical properties that substitution between members of the group will preserve the biological function of the molecule, Grantham, Science. Vol. 185, pp. 862-864 (1974). It is clear that insertions and deletions of amino acids may also be made in the above-defined sequences without altering their function, particularly if the insertions or deletions only involve a few amino acids, e.g., under thirty, and preferably under ten, and do not remove or displace amino acids which are critical to a functional conformation, (...). Analogs produced by such deletions and/or insertions come within the purview of the present invention.*" (emphasis added by the board)

7. From the the first part of the disclosure referred to in point 6.1 above, the board is satisfied that the wording "amino acid additions up to 20 amino acids, deletions up to 30 amino acids or substitutions up to 30 amino acids to the naturally occurring sequences" (i.e. including the "or" operator) in part (a) of claim 1 finds a direct basis in the application as filed. The board notes, furthermore, that the last sentence of the disclosure referred to in point 6.1 above, states that "*All of the aforesaid deletions, additions and substitutions are acceptable in*

accordance with the present invention (...)". Accordingly, the skilled person is taught that the application is based on the assumption that deletions, additions and substitutions are not mutually exclusive and can therefore occur at the same time (i.e. would support the "and/or" operator).

8. From reading the disclosure referred to in point 6.2, above, it could be argued that the disclosure referred to in point 6.1, above, is flawed when it is stated in this paragraph subsequently that "analogs may be ones in which up to about 30 amino acid residues may be deleted, added or substituted". However, from reading on to the disclosure referred to in point 6.3, above, the skilled person would again learn that the disclosed deletions, additions and substitutions are not mutually exclusive. Indeed, in that paragraph, dealing with preferred substitutions, it is unambiguously stated that "*It is clear that insertions and deletions of amino acids may also be made in the above-defined sequences without altering their function*". The skilled person would thus realise that the general references to deletions, additions or substitutions throughout the disclosure were, also in a context of substitutions not being restricted to "conservative" substitutions. Accordingly, and contrary to the argument of appellant II, the wording "amino acid additions up to 20 amino acids, deletions up to 30 amino acids and/or substitutions up to 30 amino acids to the naturally occurring sequences" is clearly and unambiguously disclosed in the application as filed.

The feature "*the same glycosylation pattern*"

9. The opposition division held that the passage on page 7, lines 3 to 8 of the application as filed formed

a basis for the contested feature in claim 1. The passage reads: "*All of the aforesaid deletions, additions and substitutions are acceptable in accordance with the present invention when the so-modified analogs that are obtained retain essentially the biological activity of the sIL-6R/IL-6 chimera composed of essentially the naturally-occurring sequences, and retain* ***essentially*** *the same glycosylation pattern of the chimera composed of essentially the naturally-occurring sequences when expressed in mammalian cells*." (emphasis added by the board). Although the opposition division acknowledged that the wording in this passage differed from the wording in claim 1 by the omission of the word "essentially", it was "*however clear that the glycosylation pattern is not a matter of precise textual definition but rather varies because it is the result of a particular process (a product by process feature), i.e. the expression in mammalian cells. The skilled reader would realise that because the claimed polypeptide is different from the parent proteins, the final glycosylation pattern cannot always be exactly identical* [to] *that of the parent polypeptides but will be exactly that produced by expression in mammalian cells, which pattern might indeed vary depending* [on] *exactly which cells were used or on the culture conditions*" (decision under appeal, point 3 of the reasons).

10. In its statement of grounds of appeal, appellant II has not explicitly contested the decision of the opposition division in the context of whether or not the terms "the same glycosylation pattern" in the wording "*said sIL-6R/IL-6 and said analogs thereof retaining the same glycosylation pattern as the naturally occurring sequences when expressed in mammalian cells*" in the

first paragraph of claim 1 as compared to the initial wording in claim 1 as originally filed ("*said sIL-6R/ IL-6 and analogs thereof being glycosylated in a similar fashion to the glycosylation of naturally occurring sIL-6R and IL-6*") extended beyond the content of the application as filed. The appellant referred in this context merely to its arguments "*presented in the opposition brief dated July 18, 2007*".

11. It is established case law of the boards of appeal (see e.g. decision T 1462/08 of 17 January 2013 and the case law reviewed in decision T 165/00 of 30 November 2000) that an appeal solely based on a simple reference to submissions made in the first instance proceedings is inadmissible, as it does not state the legal and factual reasons why the impugned decision is not correct. In the present case, the appeal of appellant II is already admissible for the fact that it deals with the impugned decision in other aspects. The simple reference to the notice of opposition dated 18 July 20107 in the context of the feature "*the same glycosylation pattern*" does not affect the general admissibility of the appeal.

12. According to Article 12(2) RPBA, the statement of grounds of appeal, which in the present case is the sole substantive submission of appellant II in these appeal proceedings, shall contain a party's complete case. They shall set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed and should specify expressly all the facts, arguments and evidence relied on. In this respect appellant II has, however, not provided any single argument as to why and to which extent the findings in the impugned decision referred to in point 9, above, should be considered wrong. The board

can neither find *ex officio* in this respect anything wrong in the impugned decision's reasoning.

13. Consequently, the board does not see any reason to deviate from the finding of the impugned decision that the expression "*the same glycosylation pattern*" in claim 1 did not constitute added matter.

14. In view of the above considerations the board accepts that claim 1 complies with the requirements of Article 123(2) EPC.

Novelty

15. The opposition division considered the disclosure of document (D9) to constitute state of the art pursuant to Article 54(1)(3) EPC. The appellants have endorsed this finding in their statements of grounds of appeal. Therefore, in view of the uncontested status of document (D9), the board can accept this fact as established by the opposition division.

16. The opposition division decided that the subject-matter of claim 1 was not novel over the fusion constructs disclosed in document (D9), Figures 1 and 2 and example 3. Claim 1 embraced analogs in which the two parts were directly linked and at the same time contained certain defined deletions and/or substitutions and/or additions, and it was not disputed among the parties that these combined deletions, substitutions and/or additions allowed for the construction of the amino acid sequence of claim 1 to structurally read on the constructs disclosed in document (D9) in as far as the naturally occurring form of IL-6R had a C-terminus at Val-356. The "linker" contained in the constructs of document (D9) merely

linked one part to the other whereby any amino acid sequence could arbitrarily be defined as a linker or conversely be considered as part of a modified sIL-6R. The feature "fused ... directly" was thus not limiting. Furthermore, the feature "*retain the same glycosylation pattern as the naturally occurring sequences when expressed in mammalian cells*" was a "product-by-process" feature and any protein meeting the structural requirements of the claim and expressed in mammalian cells fell, by definition, within the ambit of claim 1. In fact, the glycosylation pattern of a compound was not a matter of precise textual definition but rather varied as it was the result of a particular process (i.e. a product-by-process feature), i.e. the expression in mammalian cells. A skilled reader would realise that, because the claimed polypeptide was different from the parent polypeptides, the final glycosylation pattern could not always be exactly identical to that of the parent polypeptides but would be exactly that produced by expression in mammalian cells, which pattern might indeed vary depending on exactly which cells were used or on the culture conditions. The glycosylation pattern of the constructs in document (D9) had to be the same as that of the composing compounds.

17. It was not disputed by appellant I that claim 1 could be construed such that, taking into account the permitted deletions, substitutions and/or additions, a polypeptide having the amino acid sequence of the analog disclosed in document (D9) would fall within the ambit of claim 1 from the point of view of the amino acid sequence when starting from the naturally occurring form of IL-6R having a C-terminus at Val-356. The board also agrees with the opposition division in this respect.

18. In a first line of argument appellant I has however contested anew that a "linker" as contained in the constructs as disclosed in document (D9) could be considered as part of the modified sIL-6R. A "linker" had a particular function and required therefore a particular amino acid sequence (see document D30, page W562, second column, 1st full paragraph). Accordingly, the "directly fused" analogs of claim 1 excluded the presence of a linker and the disclosure of document (D9) was not detrimental to the novelty of the subject-matter of claim 1.

19. The board notes in this context, however, that neither the feature "wherein sIL-6R and IL-6 are the naturally occurring forms or are characterized by amino acid additions up to 20 amino acids, deletions up to 30 amino acids and/or substitutions up to 30 amino acids to the naturally occurring sequences and wherein said sIL-6R is fused to IL-6 directly" (emphasis added by the board) in claim 1, nor the addition "or via a peptide linker molecule which is ..." excludes, either explicitly or implicitly, the so-called direct fusions to contain in the modified sIL-6R part particular sequences which could have a function of a linker as referred to by appellant I. Appellant I's first line of argument must therefore fail. The board concludes accordingly, that the construction of the amino acid sequence of claim 1 reads on the constructs as disclosed in document (D9).

20. In a second line of argument appellant I held that the fusion proteins as disclosed in document (D9), when expressed in COS-7 cells, did not "retain the same glycosylation pattern as the naturally occurring sequences when expressed in mammalian cells" as

required by claim 1. The proteins merely had a molecular weight in the range of 70 to 75 kD, whereas the construct of the invention displayed a molecular weight of 85 kD. Furthermore, document (D25) disclosed that culture conditions could affect the glycosylation of recombinantly expressed proteins. Therefore, whereas the patent in suit disclosed how to obtain properly glycosylated proteins (e.g. paragraph [0064]), document (D9) was not enabling for such conditions. In addition, in comparison with the construct of the invention, the C-terminal region of the fusion proteins disclosed in document (D9) lacked a particular motif for N-glycosylation. Accordingly, the constructs in document (D9) could not have the same glycosylation pattern as the naturally occurring sequences when expressed in mammalian cells.

21. The board can agree with appellant II, that, for it to be meaningful, a molecular weight comparison should be conducted between the prior art constructs and the claimed constructs. Appellant I's argument is however based on a comparison with a particular compound disclosed in the patent in suit (fusion prepared in example 3) being expressed in a particular expression system. The board refers furthermore to point 8, above, in particular to the interpretation by the opposition division of the feature "retain essentially the same glycosylation pattern". Seeing that the claimed polypeptide is by definition different from the parent polypeptides, the final glycosylation pattern cannot always be exactly identical to that of the parent polypeptides but is exactly that produced by expression in mammalian cells. This pattern may also vary depending on exactly which cells were used for the expression or on their culture conditions. Accordingly, the feature "*retain the same glycosylation pattern as*

the naturally occurring sequences when expressed in mammalian cells" constitutes a "product-by-process" feature and therefore any protein meeting the structural requirements of claim 1 and being expressed in mammalian cells would comply with the "glycosylation feature". The board is therefore satisfied that the glycosylation pattern of the constructs in document (D9) is compliant with the requirement in claim 1.

22. In a third line of argument appellant I has argued that, whereas the biological activity of the compounds of claim 1 was described in paragraphs [0031] and [0032] of the patent in suit (in particular growth arrest of highly malignant mammalian cells such as F10.9 melanoma cells) and evidence for such activity was provided in example 3, document (D9) was silent on such biological activity of the disclosed fusion proteins and appellant II had not provided any evidence for such biological activity either.

23. Paragraphs [0031] and [0032] of the patent in suit read:

"[0031] *The present invention concerns a chimeric sIL-6R/IL-6 protein and biologically active analogs thereof as defined above. Such a chimeric sIL-6R/IL-6 protein produced in accordance with the present invention in mammalian cells, in particular, in human cells (see Examples 1-4 below) was found to be efficiently expressed in such cells, to be highly glycosylated, and to have potent activity on tumor cells which show no response at all to IL-6 or sIL-6R alone.* (emphasis added by the board)

[0032] *More particularly, in accordance with the present invention it has been observed (see Examples 1-3 below) that the aforesaid chimeric sIL-6R/IL-6 protein of the invention causes growth arrest of highly malignant mammalian cells such as the F10.9 melanoma cells at concentrations lower than needed when a mixture of non-fused sIL-6R and IL-6 is used. This is a particularly significant result in view of the fact that such F10.9 melanoma cells continue to grow normally when treated with only IL-6 or only sIL-6R separately, and undergo growth arrest only when exposed to relatively high dosages of a combination of non-fused IL-6 and sIL-6R.*"

24. The board notes that these paragraphs in the patent in suit do not establish a general definition of "biologically active" for qualifying the analogs as referred to in claim 1. Indeed, the passages merely refer to a particular compound exemplified in the patent in suit having a certain particular biological activity (see example 3). The examples of the patent in suit, however, disclose further biological activities of the chimeric proteins of the invention, such as growth arrest and induction of differentiation of metastatic melanoma cells (example 3), essential for engraftment of human bone-marrow transplanted cells (example 4) and protection from hepatotoxicity (see example 8). The board can therefore not concur that the patent in suit would technically restrict the person skilled in the art's understanding of "biologically active" to the particular activities referred to in paragraphs [0031] and [0032] of the patent in suit.

25. Document (D9) describes the biological activity of the fusions disclosed therein. In particular example 4 refers to the stimulation of haptoglobin expression and

the expansion and formation of colonies of human $CD34^+$-cells. Accordingly, the board is satisfied that the fusion proteins as disclosed in document (D9) are biologically active and therefore meet this feature of claim 1.

26. In view of the above considerations the board concludes that the expressed fusion constructs as disclosed in document (D9) are detrimental for the novelty of the subject-matter of claim 1 of the main request.

Auxiliary request I

Claim 1

Added matter

27. In view of the fact that claim 1 differs from claim 1 of the main request merely by the deletion of an alternative in the claim, the board accepts, for the same reasons as for claim 1 of the main request (see points 4 to 13), that claim 1 satisfies the requirements of Article 123(2) EPC.

Novelty

28. There was no dispute between the parties and the opposition division was also of the opinion that because of the omission of the "and" operator in the expression "*sIL-6R and IL-6 are the naturally occurring forms or are characterized by amino acid additions up to 20 amino acids, deletions up to 30 amino acids or substitutions up to 30 amino acids to the naturally occurring sequences and wherein said sIL-6R is fused to IL-6 directly*" in part (a) of claim 1 as compared to the wording of claim 1 of the main request, the

constructs as disclosed in document (D9) do not fall within the ambit of the claim in as far as the naturally occurring form of IL-6R was considered to have a C-terminus at Val-356. Also the board considers this fact as being established.

29. It was also not in dispute among the parties that the sIL-6R form having a sequence spanning amino acids 20 to 356 as described and applied in the patent in suit, was a naturally occurring form of sIL-6R.

30. Appellant II submitted, however, that neither of the prior art documents cited in the appeal proceedings nor any of the references cited in the patent in suit disclosed the IL-6R variant having Val-356 as C-terminal end, let alone the mechanism by which this variant was generated. Furthermore, the notion a "naturally occurring sIL-6R" was not defined in the patent in suit. Evidently, the skilled person understood the notion "naturally occurring sIL-6R" to refer to "any sequence of sIL-6R which could be found in nature". Therefore, in order to construe the subject-matter of the claims, it needed to be established what the skilled person would understand this notion to mean, in particular whether that person would also consider further naturally occurring sIL-6R forms, different from the variant spanning amino acids 20 to 356 (as used in the patent in suit), in view of the fact that such further naturally occurring forms of sIL-6R indeed existed in nature as formed by alternative splicing or "shedding" (proteolytic cleavage). The alternative splicing variant disclosed in documents (D20) and (D26) contained amino acids 20-355 followed by 10 additional amino acids at the C-terminal end. At least four shedding variants of sIL-6R existed: (i) a shedded form obtainable by induction with phorbol ester, generated

by cleavage with ADAM17 (=TACE) and comprising amino acids 20-357 (see document (D26)) or amino acids 20-336 (see document (D20)); (ii) a shedded form obtainable by cleavage with a metalloproteinase (SMP) from *Serratia marcescens*, with a C-terminus in the region ranging from Ser-320 to Thr-335 (see document (D28)); and (iii) a shedded form generated by cleavage with ADAM10, for which the cleavage site was not yet characterised (see document (D29)).

31. Of particular relevance for the novelty of the subject-matter of claim 1 was (iv) the shedded form of sIL-6R obtained through induction by pore-forming toxins as disclosed in document (D27), with a C-terminus in the region between Asn-337 and Ser-348 of IL-6R. When assuming that Ser-348 constituted the C-terminus, then the sIL-6R part of the fusion protein according to Fig. 1 of document (D9) differed from this shedded form by the absence of amino acids 324-348, i.e. by the deletion of 25 amino acids, whereby part (a) of claim 1 allowed for deletions of up to 30 amino acids in the sIL-6R part. The fusion protein disclosed in example 3 of document (D9) fulfilled accordingly the requirements of part (a) of claim 1 and was thus detrimental for the novelty of this subject-matter.

32. A similar argument to above had been submitted by appellant II in the opposition proceedings. At that time the argument was however based solely on the disclosure in document (D20). The opposition division held that document (D20) did not unambiguously disclose a naturally occurring sIL-6R which ended at amino acid 336. The argument to hold the subject-matter of part (a) of claim 1 not novel over the disclosure in document (D9) therefore failed.

33. In order to decide this contentious point, it needs to be established how the skilled person reading the patent in suit would construe the term "wherein sIL-6R is the naturally occuring form". The board notes that in paragraph [0002] of the patent in suit it is stated: "*Soluble forms of IL-6R (sIL-6R), corresponding to the extracellular domain of gp80, are natural products of the human body found as glycoproteins in blood and urine (Novick et al, 1990, 1992)*." Accordingly, the board judges that the patent in suit makes it plain to the skilled person that the naturally occurring form of sIL-6R in the context of the patent in suit are such soluble forms of glycosylated protein occurring in the blood and urine of the human body and not "*any sequence of sIL-6R which can be found in nature*" as contended by appellant II (see point 26).

34. The board acknowledges that the the prior art taught the skilled person that naturally occurring sIL-6R is formed either by alternative splicing or shedding (see e.g. document (D20), abstract, lines 3 to 4 and document (D26), page 283, right-hand column, lines 3 to 13 and 25 to 33).

35. Concerning the alternative splicing variant, both documents (D20) and (D26) appear to report that the C-terminal part ends at amino acid 355 of the transmembrane form extended by a particular 10 amino acid peptide (see document (D20), page 50, legend of figure 1, lines 4 and 5 and document (D26), Figure 3(b)). The board notes however that the (artificial) deletion of 30 amino acids from the C-terminus of this alternative splicing form (as allowed for by claim 1 part (a)) would result in a sIL-6R part ending at amino acid 335. Accordingly, when starting from this alternative splicing variant, the constructs of

document (D9), wherein the C-terminus of the sIL-6R part is at amino acid 323, would therefore not be detrimental for the novelty of the subject-matter of claim 1.

36. The board notes furthermore that the four shedding forms of sIL-6R referred to by appellant II (see points 27 and 28) are in fact all generated artificially (e.g. by *in vitro* treatment with non-natural conditions or enzymes, yeast expression, etc.) and are not reported by the authors to have been detected in blood or urine of the human body. The board considers therefore that, although these shedding forms were reported in the prior art, they would not be considered by the skilled person to constitute "naturally occurring sequences" as referred to in the patent in suit and in claim 1. Accordingly, the board cannot concur with appellant II that the shedding forms as referred to by the applicant can appropriately form the basis of a construction of claim 1, so that the fusions disclosed in document (D9) could be considered to be detrimental for the subject-matter of claim 1.

37. In view of the above considerations the board is satisfied that the subject-matter of claim 1 is novel over the fusions as disclosed in document (D9).

Claims 4-13, 17 and 18

38. In its statement of grounds of appeal, appellant II maintained the novelty objections against the subject-matter of claims 4-13, 17 and 18 as raised in the opposition proceedings. For substantiation of the objection, appellant II specifically referred *"to the explanations and arguments presented in section D.2 of our opposition brief dated July 18, 2007.*"

39. It can be taken from the minutes of the oral proceedings before the opposition division that after a discussion on the content of document (D20) in the context of claim 1 of the First Auxiliary Request, and a break for deliberation, the opposition division "*indicated that it had come to the conclusion that the OD still had doubts that the 336 variant occurs naturally and thus, the First Auxiliary Request was novel.*" (see point 36 of the minutes). Point 37 of the minutes then indicated that subsequently the opponent was invited to present arguments in relation to inventive step.

40. The board notes that from the minutes of the oral proceedings it can thus not be inferred that the opponent, in view of the finding of the novelty of the subject-matter of claim 1, in fact maintained the novelty objections against claims 4-13, 17 and 18.

41. The decision of the opposition division is in fact likewise silent on the issue of the novelty of the subject-matter of claims 4-13, 17 and 18 and concludes, after providing reasons why the subject-matter of claim 1 was novel, that the "*claims of auxiliary request 1 meet the requirements of Art. 54 EPC for novelty.*"

42. Upon appeal, appellant II has not argued that the opposition division committed a procedural violation by not dealing with the opponent's objections as to the effect that the subject-matter of claims 4-13, 17 and 18 lacked novelty, but merely made the remark that "*These novelty objections were not discussed during the oral proceedings held in the opposition proceedings.*"

43. The board considers neither, however, that in view of the finding below, it is necessary, nor appropriate for the board to rule on whether or not there was an implicit withdrawal by the opponent of the novelty objections against claims 4-13, 17 and 18 during the oral proceedings before the opposition division or whether or not the opposition division had committed one or more procedural violations by not hearing the opponent on this issue during the oral proceedings and/or not reasoning its findings on the novelty of the subject-matter of the First Auxiliary Request before them.

44. The board notes that claims 4 to 6 are directly or indirectly dependent on claim 1. Since the board has decided that the subject-matter of claim 1 is novel over the disclosure in document (D9), the subject-matter of these three claims is likewise novel over the disclosure.

45. Claims 8, 9, 12, 13, 17 and 18 are independent claims. They relate to a DNA sequence encoding a chimeric sIL-6R/IL-6 as defined in claim 1, a DNA vector comprising such a DNA sequence, transformed mammalian cells containing such a DNA vector, a method for producing a chimeric sIL-6R/IL-6 as defined in claim 1, a pharmaceutical composition comprising the chimeric sIL-6R/IL-6 and the use of such chimera for treating particular diseases, respectively. In view of the fact that the board has decided that the fusions of claim 1 are novel, DNA sequences encoding such fusions, vectors containing such, cells containing such vectors and methods for producing such fusions are also inherently novel. Accordingly, the subject-matter of claims 8, 9, 12, 13, 17 and 18 is novel over the disclosure of document (D9). Claims 10 and 11 are both dependent on

claim 9, and accordingly their subject-matter is likewise novel over the disclosure in document (D9).

46. In view of the above considerations the board decides that the subject-matter of the claims of auxiliary request 1 is novel.

Inventive step

Claim 1

47. The opposition division considered document (D1) (having the title "*A bioactive designer cytokine for human hematopoietic progenitor cell expansion*") to represent the closest prior art for the assessment of whether or not the subject-matter of claim 1 involved an inventive step. One difference between the fusion protein of sIL-6R and IL-6 disclosed in document (D1) (i.e. H-IL-6, see e.g. Fig.1B) and the claimed chimeric protein was that H-IL-6 lacked *inter alia* the Ig-like domain present in the N-terminal part of naturally occurring sIL-6R. The technical problem underlying the invention was thus the provision of an alternative "designer" cytokine. Document (D1) itself justified the absence of the Ig domain of sIL-6R in H-IL-6 so as "[t]*o keep the overall size of the fusion protein as small as possible we excluded the N-terminal Ig domain as well as the C-terminal tether domain of the human sIL-6R, which had previously been shown not to contribute to ligand binding and biological activity of the IL-6R protein*" (see page 143, left-hand column, lines 6 to 11). No other passage in document (D1) or in any other cited document provided the skilled person with a motivation to re-instate the Ig domain of sIL-6R. Accordingly, the opposition division considered the subject-matter of claim 1 to be inventive.

48. Upon appeal the parties have neither challenged the fact that document (D1) represented the closest prior art nor the technical problem as formulated by the opposition division. The board sees no reason to disagree either.

49. It therefore needs to be established whether the skilled person starting from the H-IL-6 fusion construct disclosed in document (D1) would reinstate the whole Ig domain part of IL-6R at its N-terminus in order to arrive at fusions which fall under the terms of claim 1.

50. The board concurs with the opposition division that the statement referred to on page 143 of document (D1) (left-hand column, lines 6 to 11, see point 47, above) would not motivate the skilled person to modify the H-IL-6 fusion so as to include the Ig domain in view of the firm statement in the passage that the domain was not involved in either ligand binding or biological activity of sIL-6R.

51. Appellant II submitted, however, that the passage referred to on page 143 of document (D1) was framed in the specific context of protein expression in yeast host cells and that the skilled person was aware that the expressed aim to keep the fusion protein "*as small as possible*" did not apply to expression systems other than yeast cells, such as mammalian expression systems, where there was no necessity to keep the size of the fusion protein as small as possible. Accordingly, the passage did not discourage the skilled person from modifying the fusion protein of document (Dl) by re-introducing the Ig domain or the C-terminal tether domain. Furthermore, the patent in suit itself

emphasised in the first sentence of paragraph [0005] that "*The common experience in developing recombinant proteins which can be used for treating human patients has been shown that it is important to remain as close as possible to the natural forms of the proteins, as they are found in the human body, in order to avoid triggering of antibodies and other side effects observed with non-natural recombinant products.*" Appellant II therefore held that there existed a motivation for the skilled person when embarking on providing a solution to the technical problem to (i) express the fusion protein disclosed in document (D1) in mammalian cells instead of yeast cells to obtain the natural glycosylation pattern; and (ii) to include the Ig-like domain into the sIL-6R part of the molecule so that all parts naturally present in the individual proteins were also present in the combined fusion protein. Accordingly, the skilled person would have modified the fusion protein disclosed in document (D1) in an obvious manner and arrived at a fusion protein falling within the ambit of claim 1.

52. The board considers that the passage in document (D1) on page 143, left-hand column, lines 6 to 11 (see point 38) conveys an unambiguous message to the skilled person that the N-terminal Ig domain of the sIL-6R does not contribute to the ligand binding and biological activity of the sIL-6R protein and appears therefore of no biological relevance. Also other cited documents corroborate this message. Indeed, document (D20) states on page 53, left-hand column, section "Discussion", lines 1 to 8: "*We have shown that the soluble IL-6R lacking the NH2-terminal Ig domain is fully active with respect to ligand binding and cell stimulation. Therefore, it can be concluded that the Ig region is not required for the biological function of the IL-6R.*

Similar results have been obtained with N-terminally truncated sIL-6R expressed in COS-7 cells (Yawata et al. 1993)." The latter reference to Yawata *et al.* is document (D22) in the present proceedings, which states in the paragraph bridging pages 1709 and 1710: "*Therefore, the extracellular region of IL-6R possesses two functions: IL-6 binding and association with gp130 to generate the IL-6 signal. In the present study, we demonstrate that the cytokine receptor family domain of IL-6R is responsible for both of the above functions and that the Ig-like domain is required neither for IL-6 binding nor mediating the IL-6 signal*." The board therefore concludes that the skilled person would not derive from this passage a clear pointer to include in the alternative fusions to solve the technical problem those Ig domain parts of sIL-6R.

53. Although both documents (D1) and (D20) admittedly mainly deal with yeast expression systems, document (D22) makes the statement clearly in the context of other expression systems (COS cells). Accordingly, the passage referred to in document (D1) would not be interpreted by the skilled person as being solely restricted to yeast expression systems. The board notes furthermore, and appellant II has not argued differently, that neither document (D1) nor any other document cited provided the skilled person with possible pointers or a motivation to reinstate the Ig domain of sIL-6R when embarking on solving the technical problem starting from the construct as disclosed in document (D1).

54. As to the argument of appellant II to the effect that the patent in suit in paragraph [0005] stated that it was "the common experience" that, when constructing non-natural recombinant products, it was important to

remain as close as possible to the natural forms of the proteins in order to avoid the triggering of antibodies and other side effects, the board notes that this passage in the patent in suit frames rather in the context of side effect due to improper glycosylation rather than by structural modifications.

55. Accordingly, the board cannot conclude on the basis of the arguments related to the prior art and submitted by appellant II that the decision of the opposition division that the subject-matter of claim 1 involves an inventive step is erroneous.

Claims 2 to 19

56. Claims 2 to 7 are dependent claims which are directly or indirectly dependent on claim 1. Since the board has decided that the subject-matter of claim 1 involves an inventive step, the subject-matter of these three claims likewise involves an inventive step.

57. Claims 8, 9, 12, 13, 15, 17 and 18 are independent claims which directly refer to the subject-matter of claim 1. In view of the fact that the board has decided that the artificial fusions of claim 1 involved an inventive step, the subject-matter of claims 8, 9, 12, 13, 17 and 18 also involves an inventive step with regard to the disclosure of document (D9). Claims 10, 11, 14 , 16 and 19 are claims dependent thereon and their subject-matter likewise involves an inventive step with regard to the disclosure in document (D1).

58. Appellant II has however argued that the subject-matter of claims 15, 16, 18 and 19 lacks an inventive step over the disclosure in document (D1) read in the light of document (D5). It was argued that the skilled person

was knowledgeable in the field of immunology and would know that IL-6 and the soluble IL-6 receptor can be used in the treatment of melanoma as evidenced by document (D5).

59. The board notes in this respect that document (D5) does not contribute to reverting the finding of the board that the subject-matter of claim 1 involves an inventive step, as the reason therefor was independent of the (lack of) knowledge of the skilled person on the applicability of IL-6 and the soluble IL-6 receptor in the treatment of melanoma. Accordingly, in view of the direct reference of claims 15, 16, 18 and 19 to the subject-matter of claim 1, their subject-matter involves an inventive step (Article 56 EPC).

Claim 18

60. Claim 18 is directed to the use of the subject-matter of any one of claims 1 to 5 or 8 for the preparation of a pharmaceutical composition for treating *inter alia* liver disorders.

61. Appellant II argued that, since this aspect of the claimed subject-matter could not validly claim any of the priority dates of the patent in suit but had the filing date of 9 July 1998 as the relevant date, document (D9) was contained in the prior art pursuant to Article 54(2) EPC. Document (D9) disclosed the fusion proteins of claim 1 and further that such fusion proteins upon administration have medical applications. Example 4 (page 8, line 28 to page 10, line 12) demonstrated in particular that the fusion proteins were capable of inducing haptoglobin expression and secretion in hepatoma cell lines and hence that liver cells were a potential target for fusion proteins

comprising sIL-6R and IL-6. Based on this information it was obvious to the skilled person to use the fusion proteins for the treatment of haptoglobin-deficiency or other liver disorders. Consequently, the subject-matter of claim 18 did not involve an inventive step with regard to the disclosure in document (D9).

62. In point 37, above, the board concludes that the fusions as subject-matter of claim 1 are novel over the disclosure in document (D9). The argument of appellant II starts however from the premise that document (D9) does impair the novelty of the subject-matter of claim 1. The board notes therefore that appellant II has not presented any argumentation as to the effect that, starting from document (D9) as representing the closest prior art, the subject-matter of claim 1 does not involve an inventive step. Already for this reason therefore the argument of appellant II must fail.

63. The board notes moreover that appellant I has submitted that the reference to the stimulation of haptoglobin expression in example 4 of document (D9) would not have led the skilled person to conclude that the fusion proteins were useful for the treatment of liver diseases as none of the common liver diseases was characterised by a reduced expression of haptoglobin (which was synthesised in the liver). It was submitted that actually, a reduced haptoglobin level could be indicative of hemolysis, unrelated to a liver dysfunction. Furthermore, the increased haptoglobin level that was found in various cancers did certainly not call for stimulation of haptoglobin expression.

64. In this context the board notes that appellant II has not filed any documentary evidence to the effect that

the capacity of a compound to induce haptoglobin expression and secretion in hepatoma cell lines is useful for treating liver disorders. Also in this respect the argument of appellant II must fail.

65. In view of the above considerations the board deems it not necessary to rule on whether or not the filing date of the patent in suit is the effective date of the contentious subject-matter of claim 18.

66. Taking the above considerations into account the board decides that the subject-matter of the claims of auxiliary request I involves an inventive step.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairwoman:

D. Hampe G. Alt

Decision electronically authenticated