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Datasheet for the decision of 21 October 2009

Case Number: T 0018/09 - 3.3.08

Application Number: 96939612.6

Publication Number: 0939804

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
NEUTROKINE alpha

Patentee:
HUMAN GENOME SCIENCES, INC.

Opponent:
ELI LILLY AND COMPANY

Headword:
Neutrokine/HUMAN GENOME SCIENCES

Relevant legal provisions:
EPC Art. 123(2)(3), 84, 83, 54, 56, 57

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request - added subject-matter (no); extension of protection (no); clarity (yes); sufficiency of disclosure (yes); industrial application (yes); novelty (yes); inventive step (yes)".

Decisions cited:
G 0001/92, T 0301/87, T 0381/87, T 0019/90, T 0890/02, T 0870/04, T 0898/05

Catchword:

(1) In case of parallel proceedings before a national court and the Boards of Appeal, parties should inform both tribunals of the position as early as possible and ask the appropriate tribunal for acceleration in order to avoid duplication of proceedings. Whether acceleration is requested by one party, or both or all parties in agreement, or by a national court, all parties must accept a strict procedural framework including short time limits. It must also be understood that acceleration can have no effect on the equal treatment of all parties and cannot confer any advantage on any one party (see points 1 to 3 of the Reasons).

(2) An objection of lack of industrial application (Article 57 EPC) requires the same standard of proof as an objection of insufficient disclosure (Article 83 EPC), namely serious doubts substantiated by verifiable facts (see points 31 to 33 of the Reasons).

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0018/09 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 21 October 2009

Appellant: (Patent Proprietor)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 3 December 2008 revoking European patent No. 0939804 pursuant to Article 101(2),(3)(b) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: P. Julià
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent No. 0 939 804, based on European patent application No. 96 939 612.6, was granted with 27 claims. Three oppositions were filed on the grounds as set forth in Articles 100(a),(b) and (c) EPC. Opponents 02 and 03 both withdrew their oppositions by letters dated 15 October 2007.

II. Claims 1 and 20 as granted read as follows:

"1. A nucleic acid molecule comprising a polynucleotide sequence encoding a Neutrokine-α polypeptide wherein said polynucleotide sequence is selected from the group consisting of:

(a) a polynucleotide sequence encoding the full length Neutrokine-α polypeptide having the amino sequence of residues 1 to 285 of SEQ ID NO:2;

(b) a polynucleotide sequence encoding the extracellular domain of the Neutrokine-α polypeptide having the amino acid sequence of residues 73 to 285 of SEQ ID NO:2;

(c) [...]

(d) [...]

(e) [...]

(f) [...]".

"20. An antibody or portion thereof that binds specifically to the Neutrokine-α portion of a Neutrokine-α polypeptide having the amino acid sequence encoded by the nucleic acid molecule of any one of claims 1(a) through 1(f) or 7 or the Neutrokine-α portion of a Neutrokine-α polypeptide of claim 15 or 16."

III. In its decision dated 3 December 2008, the opposition division considered the main request (claims as granted) to contravene Article 123(2) EPC and a first auxiliary request not to fulfil the requirements of Article 56 EPC. A second auxiliary request was not admitted into the proceedings. Accordingly, the patent was revoked.

IV. On 30 December 2008, the patentee (appellant) filed a notice of appeal.

V. Opponent 01 (respondent) had also commenced proceedings in England against the appellant seeking a declaration that the patent was invalid. The first instance decision in those proceedings, issued on 31 July 2008, held that the patent was invalid for lack of industrial application, insufficiency and lack of inventive step (see *Eli Lilly and Company v. Human Genome Sciences, Inc.* [2008] EWHC 1903, paragraph 327, document D115 in the present appeal proceedings). The appellant also filed an appeal against that national court decision. When the present appeal to the board of appeal was commenced, the national appeal was pending before the Court of Appeal of England and Wales and was scheduled to be heard in July 2009.

VI. On 22 January 2009 the board received a request from the national court to accelerate the proceedings in order to dispose of the present appeal before the hearing of the appeal in the parallel English proceedings. The national court informed the board that the parties were in agreement with the acceleration

request (see *Eli Lilly and Company v. Human Genome Sciences, Inc.* [2008] EWCA Civ 168, paragraph 4).

VII. On 6 February 2009 the board issued a communication to the parties informing them that it would only be possible to give effect to the national court's request if they would agree that the time limits for filing the written statement of grounds of appeal and reply be at least halved and enclosing a schedule proposing a timetable and other directions based on such abridged time limits which would lead to oral proceedings on 17 and 18 June 2009. The parties were directed to inform the board, by no later than 16 February 2009, that they agreed to adhere to that timetable and told that, if so agreed, the schedule would take immediate effect and the summons to oral proceedings would be issued immediately thereafter; however, if either party did not so agree, the usual time limits would apply. The board sent a copy of its communication to the national court.

VIII. The appellant replied by fax on 12 February 2009 that it supported the proposal and agreed to oral proceedings on 17 and 18 June 2009 but "subject to the agreement of an acceptable timeline for written submissions". The only indications as to what time it would consider "acceptable" were the statements that it could not file its statement of grounds of appeal by the suggested date of 28 February 2009 but would use its best endeavours to submit the statement "as much before the 13 April 2009 deadline as possible" (13 April 2009 being the due date in the absence of acceleration).

IX. The respondent replied by fax also on 12 February 2009 agreeing the timetable proposed by the board and, in a further fax of 13 February 2009, it answered the appellant's submission by observing that, if the statement of grounds of appeal was not filed until or shortly before 13 April 2009, the even shorter time it would have to prepare and file an appropriate reply would be neither adequate nor equitable.

X. In a further communication to the parties of 18 February 2009 the board informed them that, in view of the situation, the usual time limits would apply. The board also informed the national court (to which a copy of the communication was sent) that its request for acceleration of this appeal could not be met.

XI. On 18 February 2009, the national court asked the board for its best estimate of when it could hold oral proceedings on the basis that the previously proposed dates of 17 and 18 June were not possible. The board replied on 19 February 2009 that its best estimate was late October 2009 if the parties did not agree to any reduction in time for their written submissions and early September 2009 if the parties should agree to such reduced time. On 23 February 2009, a hearing took place in the national court at which the national court postponed its own hearing from July 2009 to December 2009. The parties in the present proceedings were invited by the national court to co-operate with the board about fixing a date for oral proceedings as soon as possible (see *Eli Lilly and Company v. Human Genome Sciences, Inc.* [2008] EWCA Civ 168, paragraphs 12 to 14). Oral proceedings were subsequently appointed for 20 and 21 October 2009.

XII. On 13 April 2009, the appellant filed a statement setting out its grounds of appeal together with a new main request, 16 auxiliary requests and further documentary evidence (documents D115 to D162).

XIII. In a letter dated 1 May 2009, the respondent requested the board not to admit the appellant's claim requests and new documents into the proceedings. On 25 May 2009, the appellant filed written arguments for the admissibility of both the new documents and claim requests.

XIV. On 23 July 2009, the respondent filed its reply to the appellant's grounds of appeal and filed seven new documents (documents D163 to D169).

XV. On 31 July 2009, the appellant filed documents D170 to D173 and commented on the respondent's reply.

XVI. The board sent a communication to the parties on 24 August 2009 informing them of its preliminary, non-binding opinion on substantive issues.

XVII. In letters dated 30 September 2009, both appellant and respondent replied to the communication of the board. The appellant filed a new main request, auxiliary requests I to V and documents D174 to D190. The respondent filed two new documents.

XVIII. Oral proceedings took place on 20 and 21 October 2009. During the oral proceedings, the appellant withdrew all its previous requests and filed a **new main request**. The respondent withdrew its request that the new documents

filed by the appellant during the appeal phase not be admitted.

XIX. Claims 1, 6 and 13 of the **main request** at issue read as follows:

"1. An isolated nucleic acid molecule comprising a polynucleotide sequence encoding a Neutrokine-α polypeptide wherein said polynucleotide sequence is selected from the group consisting of:
(a) a polynucleotide sequence encoding the full length Neutrokine-α polypeptide having the amino sequence of residues 1 to 285 of SEQ ID NO:2; and
(b) a polynucleotide sequence encoding the extracellular domain of the Neutrokine-α polypeptide having the amino acid sequence of residues 73 to 285 of SEQ ID NO:2."

"6. A recombinant vector containing an isolated nucleic acid molecule consisting of a polynucleotide sequence encoding a Neutrokine-α polypeptide wherein said polynucleotide sequence is selected from the group consisting of:
(a) a polynucleotide sequence encoding the full length Neutrokine-α polypeptide having the amino sequence of residues 1 to 285 of SEQ ID NO:2; and
(b) a polynucleotide sequence encoding the extracellular domain of the Neutrokine-α polypeptide having the amino acid sequence of residues 73 to 285 of SEQ ID NO:2."

"13. An isolated antibody or portion thereof that binds specifically to

(g) the full length Neutrokine-α polypeptide (amino acid sequence of residues 1 to 285 of SEQ ID NO: 2); or

(h) the extracellular domain of the Neutrokine-α polypeptide (amino acid sequence of residues 73 to 285 of SEQ ID NO: 2)."

Claims 2 to 4 related to embodiments of claim 1, and claim 5 to a method of making a recombinant vector comprising inserting the nucleic acid molecule of any one of claims 1 to 4 into a vector. Claim 6 together with dependent claim 7 concerned a recombinant vector containing said isolated nucleic acid molecule. Claim 8 related to a method of making a recombinant host cell by introducing the vector of claim 6 or 7 and claim 9 was directed to a mammalian host cell genetically engineered with the recombinant vector of claim 6 or 7. Claim 10 related to an isolated Neutrokine-α polypeptide consisting of the amino acid sequence of either residues 1 to 285 or residues 73 to 285 of SEQ ID NO:2. Claims 11 and 12 related to embodiments of claim 10. Claim 13 together with dependent claims 14 to 17 were concerned with an isolated antibody or portion thereof binding specifically to the Neutrokine-α polypeptide defined as in claim 10. Claim 18 was directed to a pharmaceutical composition comprising the polypeptide of any one of claims 10 to 12, or the antibody or portion thereof of any one of claims 13 to 17. Claim 19 was directed to a diagnostic composition comprising the nucleic acid molecule of claims 1 to 4 or the polypeptide of claims 10 to 12 or the antibody of claims 13 to 17.

XX. The documents referred to in the present decision are:

D1: H-J. Gruss and S.K. Dower, Blood, 15 June 1995, Vol. 85(12), pages 3378 to 3404;

D2: EST D79690 (created on 7 February 1996) EMBL-ENI database;

D3: P.A. Moore et al., Science, 9 July 1999, Vol. 285, pages 260 to 263;

D10: P. Schneider et al., J. Exp. Med., 7 June 1999, Vol. 189(11), pages 1747 to 1756;

D22: EST NCBI-GenBank Acc R16882, IMAGE Clone ID 129696, April 1995;

D24: EST NCBI-GenBank Acc T87299, IMAGE Clone ID 115371, March 1995;

D25: A. Mukhopadhyay et al., J. Biol. Chem., 4 June 1999, Vol. 274(23), pages 15978 to 15981;

D31: H-J. Gruss, J. Clin. Lab. Res., September 1996, Vol. 26, pages 143 to 159;

D32: S.R. Wiley et al., Immunity, December 1995, Vol. 3, pages 673 to 682;

D34: EST NCBI-GenBank Acc AA682496, IMAGE Clone ID 450662, 4 April 1996;

D39: Alignement of EST D79690 with Seq.ID NO:2, 9 April 2003;

D48: Alignement of EST R16882 and EST G30081 with Seq.ID NO:1, 9 April 2003;

D50: Alignement of EST T87299 with SEQ.ID NO:1, 9 April 2003;

D52: Declaration of Dr D.E. Cash dated 6 March 2008;

D75: Declaration of Dr S. Farrow dated 25 March 2008;

D84: Declaration of Dr K.K. Kikly dated 1 April 2008;

D85: Expert report of Dr R. Apweiler dated 29 May 2007;

D86: W.R. McCombie et al., Nature Genetics, May 1992, Vol. 1, pages 124 to 131;

D115: Eli Lilly and Company v. Human Genome Sciences, Inc. [2008] EWHC 1903;

D126: L. Fu et al., Blood, 2006, Vol.107(11), pages 4540 to 4548;

D140: B. Huard et al., J. Immunol., 2001, Vol. 167, pages 6225 to 6231;

D150: US 7,317,089 (publication date: 8 January 2008);

D173: Press release of Human Genome Sciences and GlaxoSmithKline of 20 July 2009;

D175: Second declaration of Dr G.H. Kelsoe III dated 29 September 2009.

XXI. The appellant's arguments may be summarised as follows:

Article 84 EPC

The term "isolated" was introduced into the claims to overcome an objection raised by the opponent and its meaning was given in paragraph [0044] of the patent-in-suit. Claim 6 only took over the wording of claim 1.

Article 123(3) EPC

Since granted claim 1 comprised fusion proteins, the term "portion" in granted claim 20 intended to exclude antibodies raised against known proteins when fused to the Neutrokine-α polypeptide. That term was different from the term "epitope-bearing portions" used in the patent-in-suit to define fragments of the Neutrokine-α polypeptide. The meaning of "portion" in the context of granted claim 20 was clearly understood by the skilled person. Thus, the omission of that term in claim 13 did not make its scope broader than that of granted claim 20, the claimed antibody being in both cases one that binds to Neutrokine-α.

Article 54 EPC

Documents D48 and D50 showed that the sequences of the IMAGE clones disclosed in documents D22 and D24 (clones 129696 and 115371) aligned imperfectly with that of Neutrokine-α. Even if the actual sequences of these

clones were identical to that of Neutrokine-α (as stated in Dr Kikly's declaration, D84), documents D22 and D24 did not contain any explicit information on the relevant part of these sequences so as to make them directly available to the skilled person. Moreover, neither of these two clones was recognisably made available to the public, since the public did not have access to them without undue burden. The IMAGE Consortium Library comprised a multitude (about 540,000) of randomly collected and numbered cDNA clones derived from more than 20 sources. Many of these clones were incomplete and contained cloning artefacts, and there was no method to identify an IMAGE clone as a potential member of the TNF ligand superfamily other than screening and sequencing all clones of the IMAGE Consortium Library. An uncharacterized clone within a library of thousands of other uncharacterized clones could not be compared with an indexed book in a library. Whereas a book could be interrogated by the public using direct mental procedures, interrogation of the uncharacterized clones of the IMAGE Consortium required physical manipulation and biochemical sequencing of each clone, using methods susceptible to errors, followed by a highly complex bioinformatic analysis where the results depended on numerous parameters. The information required to identify any of the IMAGE clones was not provided by an arbitrary and meaninglessly identification number. The mere deposition of these clones in the IMAGE Consortium Library did not make them available to the public, since they were all anonymous and indistinguishable.

Articles 83 EPC

The disclosure of the nucleic and amino acid sequences of Neutrokine-α allowed the skilled person to perform the claimed embodiments without undue burden, including the claimed diagnostic and pharmaceutical compositions. The identification of Neutrokine-α as a member of the TNF ligand superfamily made it a plausible and promising candidate for stimulating and/or inhibiting immune responses. Neutrokine-α expression in B-cell and T-cell lymphomas and on activated T-cells supported the use of anti-Neutrokine-α antibodies to treat these lymphomas and the detection of activated T-cells using Neutrokine-α as a marker. Methods to produce, screen and select antibodies of interest were known in the art and post-published documents on file showed that no problems were found in their production. These documents further confirmed the uses predicted in the patent-in-suit.

Article 57 EPC

Based on structural features, the patent-in-suit identified Neutrokine-α as a new member of the TNF ligand superfamily. All members of that superfamily had a diagnostic and therapeutic interest since they were known to play a central role in human diseases as a result of their involvement in the regulation of human immune cells. Although they had pleiotropic effects, the members of that superfamily were not so diverse that a skilled person could not derive a function for a novel member. Indeed, all members shared significant biological effects on the immune system, with the ability to both stimulate and inhibit the growth,

proliferation and differentiation of immune cells. They were known to be implicated in a number of diseases of the human immune system, which was known to be highly complex and to involve multiple classes of molecules. Thus, it was not surprising to expect a novel member of that superfamily to have different, and even opposite, biological effects on the immune system depending on the type of immune cell and its activation stage. The list of possible Neutrokine-α activities and effects on diseases and conditions cited in the patent-in-suit reflected only the activities, diseases and conditions common to the known members of the TNF ligand superfamily and expected to be shared by a new member of that superfamily.

All members of the TNF ligand superfamily were known to be expressed on activated T-cells and to co-stimulate T-cell proliferation. Thus, the skilled person expected a new member of that family to have these activities (*inter alia* documents D1 and D31). Indeed, the patent-in-suit showed the expression of Neutrokine-α mRNA in activated T-cells and the activity of Neutrokine-α in directing the proliferation, differentiation and migration of monocytes, lymphocytes and neutrophils. Post-published evidence confirmed that activity of Neutrokine-α as well as T-cell co-stimulation and the presence of Neutrokine-α on the surface of activated T-cells. Only standard assays were required to detect the presence of Neutrokine-α on activated T-cells and, as shown by the references cited in the background art of the patent-in-suit, to measure T-cell co-stimulation.

The patent-in-suit disclosed Neutrokine-α expression in B-cell and T-cell lymphomas thereby providing an

"immediate concrete technical benefit" (cf e.g. T 898/05 of 7 July 2006), namely the use of Neutrokine-α (or antibodies thereto) to image, diagnose and/or treat these lymphomas. All the more so because other members of the TNF ligand superfamily were known to be implicated in the pathology of lymphoma and were identified as relevant targets for use in the diagnosis and/or treatment of these lymphomas. The expression of Neutrokine-α in B-cell and T-cell lymphomas made it reasonable to expect the presence of Neutrokine-α on the surface of those lymphomas, since mRNA expression was accepted to be correlated with protein expression and type II transmembrane proteins were usually found at cell surface. There was also post-published evidence on file confirming Neutrokine-α expression in lymphoma and its presence on their cell surface. Cellular non-specificity with associated undesired side effects was a hallmark of most known chemotherapeutic anti-lymphoma agents. Lymphomas were also known to be more susceptible to radio-immunotherapy than other solid tissues that, contrary to lymphomas, could repair radiation damage. Therefore, the absence of information in the patent-in-suit on the relative levels of Neutrokine-α in non-lymphoma and lymphoma cells and the apparent widespread distribution of Neutrokine-α mRNA did not preclude a possible use of Neutrokine-α (or antibodies thereto) as an imaging, diagnostic or therapeutic agent.

Article 56 EPC
Document D1 as closest prior art

The closest prior art was document D1 and the technical problem to be solved was the provision of a further

member of the TNF ligand superfamily. Based on structural features and other (functional) information disclosed in the patent-in-suit, Neutrokine-α was plausibly identified as a member of that superfamily. Post-published documents confirmed the predictions of the patent-in-suit. The technical problem was thus solved. Evidence on file showed that the screening of available cDNA databases using i) full-length sequences of some members of the TNF ligand superfamily disclosed *inter alia* in documents D1 or D31, ii) a (50 residues) fragment of their conserved C-terminal sequence, or iii) a consensus sequence based upon the portion of ß-pleated sheet most conserved across these known members (D strand motif), failed to identify an EST sequence encoding Neutrokine-α (such as that of document D2). Post-published documents showed that improved profile searches and/or cDNA libraries were required to identify Neutrokine-α. Thus, the claimed subject-matter was not derivable in an obvious manner from any combination of prior art documents.

Document D2 as closest prior art

The closest prior art was defined in the case law as a document conceived for the same purpose as the claimed invention. A prior art document did not qualify as closest prior art merely because of an alleged structural similarity. Even if, using impermissible hindsight as the respondent had done, the EST sequence of document D2 was known to share structural similarities with Neutrokine-α, it could not qualify as closest prior art since it did not have the same purpose as the claimed invention. Document D2 only disclosed a bare, uncharacterized EST sequence from

about 390,000 human ESTs of the GenBank release 97 and it did not provide any information that suggested it would encode a novel member of the TNF ligand superfamily. The EST sequence of document D2 could be identified as a member of the TNF ligand superfamily only using hindsight (i.e. with knowledge of the sequence of the claimed invention), after arbitrarily selecting a unique combination of computer programs, parameters and evaluation criteria.

Document D34 as closest prior art

Dr Cash in his declaration D52 showed that document D34 was published after the filing date of the patent-in-suit and thus it was not prior art. Even if it had been available, the reasons given for the EST sequence of document D2 applied to the IMAGE clone of document D34. A document could not qualify as closest prior art based solely on alleged structural similarities that could only be determined with knowledge of the claimed invention.

Pipeline screening

An automated "pipeline screening approach" amounted to nothing more than an expansion of the "EST approach" so as to include all 390,000 ESTs available at GenBank at the filing date of the patent-in-suit and was thus exponentially more complicated and time consuming than the "EST approach". The automated "pipeline screening approach" involved hindsight (unique combination of arbitrarily selected computer programs, parameters and evaluation criteria) and required a large number of computers, capital investment and human resources.

Indeed, the limitations (filters) suggested for simplifying that approach (search only newly or daily deposited ESTs, removal of ESTs assigned to known genes, etc) required the development of new computer programs, automated processes and evaluation criteria that, apart from using impermissible hindsight, were far removed from the routine procedures available to the skilled person and his normal abilities as defined in the case law.

XXII. The respondent's arguments may be summarised as follows:

Article 84 EPC

According to the patent-in-suit (cf. paragraph [0044]), a nucleic acid molecule contained in a vector was to be considered as "isolated". The term "isolated" in the context of claim 6 rendered the scope of the claim ambiguous because it could be interpreted as implying something more than what was meant by the definition given in the patent specification. It was unclear whether, by the presence of that term, neighbouring sequences of the vector were intended to be excluded or whether those sequences or parts thereof could be comprised within the (isolated) nucleic acid molecule.

Article 123(3) EPC

The term "Neutrokine-α polypeptide" in granted claim 1 (a) to (f) did not encompass fusion polypeptides since it was defined by reference to specific SEQ ID NOs. Thus, the reference in granted claim 20 to "the Neutrokine-α portion of a Neutrokine-α polypeptide having the amino acid sequence encoded by the nucleic

acid molecule of any of claims 1(a) through 1(f)" could only mean a portion of the whole sequence of Neutrokine-α. Moreover, the reference in granted claim 20 to claims 7 and 16 indicated that the antibodies of claim 20 were directed against Neutrokine-α portions that did not include the transmembrane and/or the intracellular domain. Even if the meaning of "Neutrokine-α portion" in granted claim 20 was to be considered ambiguous, it certainly meant less than the whole sequence of the Neutrokine-α polypeptide. Thus, the omission of the term "portion" in claim 13 of the main request led to an inadmissible extension of the scope of protection, since the claim now included antibodies directed against the whole sequence of Neutrokine-α, including the transmembrane and the intracellular domain.

Article 54 EPC

The mere size of the IMAGE Consortium collection (about 540,000 clones) did not itself determine whether or not a particular clone had been made available to the public. It was established case law that a book on the shelves of a library was made available to the public, even though it was one in a collection of many millions of books (cf. T 381/87 OJ EPO 1990, 213). Whereas a DNA fragment in Lawn's gene bank could not be specifically and directly retrieved because it was mixed with all other DNA fragments in a library with nothing to distinguish them (T 301/87, OJ EPO 1990, 335), any IMAGE clone could be specifically and directly retrieved by reference to its allocated number which referred to its position in a particular well of a particular plate. Accordingly, the IMAGE clones of

documents D22 and D24 (respectively, clones 129696 and 115371) were part of the state of the art. The declaration of Dr Kikly D84 showed that the nucleic acid sequences of these two IMAGE clones encoded, respectively, amino acid residues 68 to 285 and 59 to 285 of Neutrokine-α. Although the sequences shown in documents D22 and D24 contained errors, the skilled person was well aware of their possible presence, since it was known that EST sequencing did not have to be accurate in order to serve its purpose. The correct nucleic acid sequences of these two IMAGE clones were also state of the art since these clones as such were available to the public and could be sequenced using standard technology, irrespective of whether or not particular reasons could be identified for their sequencing (cf. in this respect G 1/92, OJ EPO 1993, in particular page 277).

Article 83 EPC

Insofar as no therapeutic and/or diagnostic use for Neutrokine-α was disclosed in the patent-in-suit, the compositions of claims 18 and 19 were not enabled, even though they could be made by the skilled person. There was no disclosure in the patent-in-suit of a disease that could be diagnosed and/or treated using Neutrokine-α nor an explanation as to how a nucleic acid encoding Neutrokine-α could be used for diagnosis. Claim 13 embraced both antibodies useful for therapy and/or diagnosis and antibodies that were not suitable for these uses. For the latter antibodies, the patent-in-suit failed to provide an indication of any industrial application (*infra*). In order to be of therapeutic relevance, the former antibodies had to be

capable of blocking the Neutrokine-α activity. However, the patent-in-suit failed to disclose any Neutrokine-α activity and there was no information as to whether Neutrokine-α was active in a membrane-bound form or in soluble form. Antibodies binding to one form did not necessarily bind the other form. The patent specification did not disclose any disease in which the level of Neutrokine-α expression was increased or reduced and, even if such a disease was identified, the patent-in-suit did not teach how to prepare an antibody which was sufficiently specific to Neutrokine-α to be useful in diagnosis and/or therapy.

Article 57 EPC

On the basis of the structural information disclosed in the patent specification, it could be plausibly assumed that Neutrokine-α was a member of the TNF ligand superfamily. However, none of the claimed products (namely the isolated full-length Neutrokine-α and the extracellular domain of Neutrokine-α, residues 73 to 285 of SEQ ID NO:2) occurred in nature as such. Neutrokine-α was either present on the cellular membrane or proteolytically cleaved in the cell to a soluble form that was known to be the relevant biological form (namely, residues 134 to 285 of SEQ ID NO:2). No predictions could be validly made as to the biological activities of the claimed non-natural forms of Neutrokine-α, especially in view of the fact that the patent-in-suit did not provide any experimental data for the claimed Neutrokine-α forms.

All members of the TNF ligand superfamily (except for TNF-α and TNF-β) had their own receptor and interacted

with one-to-one correspondence. Thus, a new member of that superfamily was expected to bind to an unknown receptor and to have a novel combination of properties. Prior art on file (cf. *inter alia* documents D1 and D31) showed that known members of the TNF ligand superfamily differed dramatically in their properties, having very different effects on different cell types and at different stages of cell activation. Their function was complex, diverse and only incompletely understood. This precluded the identification of an immediate concrete application for a new member without supporting data. The patent specification failed to provide these data, since its disclosure was so broad and contradictory that it was technically meaningless.

The assertions made in the patent-in-suit, in particular about the Neutrokine-α activity on leukocytes (including lymphocytes), were not supported by any evidence. The skilled person when reading the patent-in-suit would inevitably have inferred that Neutrokine-α had not actually been expressed, let alone tested for its biological properties. This was conceded by the patent itself when stating that Neutrokine-α was merely believed to have similar activities to TNF and related cytokines. Based on these speculations, the patent specification recited a highly implausible long list of diseases, which were said to be treatable with Neutrokine-α, and a similarly implausible list of alleged uses for Neutrokine-α antagonists, which in many cases were self-contradictory (enhancing or suppressing, promoting or inhibiting). These deficiencies were not remedied by reference to standard assays or to the common general knowledge since, as shown by post-published documents, Neutrokine-α

activity was identified only on B-cells which was not mentioned in the patent, and only much later was the co-stimulatory effect of Neutrokine-α on T-cells reported, although only under very particular assay conditions not disclosed in the patent. The appellant had done what patentees without evidence of treatable conditions do when filing patent applications, namely include as "boiler-plate" the disclosure of a long list of possible activities and conditions (including implausible, self-contradictory ones) from which they later "cherry-pick" the very few which have been subsequently confirmed or demonstrated.

Although all members of the TNF ligand superfamily co-stimulated T-cell proliferation, the patent-in-suit was completely silent on that activity. Contrary thereto, it referred to a possible use of Neutrokine-α to inhibit T-cell proliferation. Thus, in the light thereof, that activity was not made plausible for Neutrokine-α. Indeed, whereas the authors of document D3 (the inventors of the patent-in-suit) failed to detect any activity of Neutrokine-α on T-cells, other post-published documents showed that the co-stimulation of T-cells by Neutrokine-α was not achieved in a straightforward manner (certainly not by using the standard assays cited in the specification) and it was still unclear whether or not that activity was real. Moreover, even if effects on T-cells were detected in an artificial *in vitro* system for some or all members of the TNF ligand superfamily, that was neither an indication of a unique or predominant activity in a complex biological system nor a pointer to a possible therapeutic or diagnostic application. Even today, the alleged Neutrokine-α T-cell co-stimulation was of no

biological significance and, even if an industrial application was found for a T-cell co-stimulating molecule, that application could not apply to the limited (if any) T-cell activity of Neutrokine-α. There was nothing in the patent-in-suit connecting an industrial application with T-cell co-stimulation or with an inhibition of that activity.

The disclosure of Neutrokine-α mRNA expression in activated T-cells was irrelevant for the purpose of industrial application since the activity and effects of Neutrokine-α were achieved only through its receptor and no information was provided on that receptor or on where, or on which cells, that receptor was located. It was also noted that the presence of Neutrokine-α on activated T-cells was not detected in document D3. Even though the patent-in-suit disclosed Neutrokine-α mRNA expression in B-cell and T-cell lymphomas (although without providing any experimental evidence), it did not report the presence of Neutrokine-α on the surface of those lymphomas (cell surface antigen) or the relative levels of that expression when compared to those in other tissues, in particular in non-cancerous B-cells and T-cells. Indeed, the patent-in-suit left it open whether the level of expression in cancerous cells was higher or lower than in the corresponding non-cancerous cells. Furthermore, since Neutrokine-α expression was disclosed *inter alia* in kidney, lung and smooth muscle tissue, a skilled person was to conclude that the use of anti-Neutrokine-α antibodies was not safe for diagnostic or therapeutic purposes. All the less so, since no information was provided on the relevance and the effects of the possible soluble forms

of Neutrokine-α on these diagnostic and therapeutic applications.

Article 56 EPC
Document D1 as closest prior art

According to established case law, the mere provision of a new protein having certain sequence characteristics did not support *per se* an inventive step if those characteristics did not lead to a specific, useful technical effect. Starting from document D1 as the closest prior art, the technical problem to be solved was the provision of a further member of the TNF ligand superfamily having at least one demonstrated or inferred technical effect that made that new member useful. Although, based on structural features, the patent-in-suit identified Neutrokine-α as a plausible new member of the TNF ligand superfamily, it failed to disclose any specific, useful technical effect for Neutrokine-α and, since that technical effect could not be derived from the TNF ligand superfamily in view of the extreme diversity in the physiological properties of its members, the patent-in-suit did not solve the technical problem as stated above.

Document D2 as closest prior art

The EST clone of document D2, even though one out of thousands of ESTs in the EMBL/GenBank/DDBJ databases, was part of the art and available to the skilled person. Indeed, EST databases were known to the skilled person as well as their use to identify new genes, the related encoded proteins and their biological functions (cf.

T 890/02, OJ EPO 2005, 497). Every EST clone was a valid starting point to identify the gene and protein to which the clone was related. Evidence on file (cf. *inter alia* document D86) showed that the characterization of (random) ESTs without having any particular gene or target in mind was also common practice in the art. The subsequent identification of a given known EST (cf. document D2) as a new member of a known protein family (TNF ligand superfamily) did not render the original EST clone unavailable as state of the art and it could not be retrospectively argued that inappropriate hindsight was required to take that particular EST clone as starting point. Accordingly, it was legitimate to ask whether the claimed invention was obvious to the skilled person having regard to document D2.

Starting from document D2 as closest prior art, the technical problem to be solved was the identification of the gene from which the EST clone of that document derived. At the filing date of the patent-in-suit, it was obvious to identify the source of an EST by searching commercially available protein databases such as Swiss-Prot. Evidence on file (cf., for example, the expert report of Dr Apweiler, D85) showed that, with standard sequence analysis techniques, the skilled person would have been able to identify the sequence of the EST clone of document D2 as a (partial) sequence of a new member of the TNF ligand superfamily (document D39 showed that it encoded residues 222 to 281 of SEQ ID NO: 2 of the patent-in-suit). The use of that EST sequence to retrieve the full-length Neutrokine-α sequence was obvious and within the abilities of the skilled person.

Document D34 as closest prior art

Although the declaration of Dr Cash D52 allegedly showed that the IMAGE clone of document D34 was not available at the filing date of the patent-in-suit, it nevertheless confirmed that this clone was provided to Washington University explicitly for the purpose of sequencing it. No inventive skill was required to perform such a sequencing, to run the resulting sequence against the Swiss-Prot database and to identify it as a new member of the TNF ligand superfamily with any of the available computer programs.

Pipeline screening

The complete IMAGE Consortium clone collection could be taken as closest prior art. It was obvious for the skilled person to look at each and every EST available in the art or, alternatively, to randomly select those ESTs, and try to identify new genes. Indeed, that was the technical problem to be solved. There was evidence on file (such as document D86) showing that "database mining" was a standard method at the filing date of the patent-in-suit for correlating new ESTs with known protein sequences of the Swiss-Prot database. A number of well-known techniques were also available to the skilled person to increase the efficiency of that searching, such as to look only at newly deposited ESTs (added to DDBJ/EMBL/GenBank on a daily basis), to select human ESTs, to filter out ESTs belonging to a comparatively small group of highly expressed known proteins and to eliminate ESTs belonging to already known genes. Using these techniques, a search would

have taken the skilled person only a few minutes and the small number of TNF-related hits could then be quickly and easily examined in a CLUSTAL multiple alignment. The skilled person also knew how to select appropriate parameters (such as e-value cut-offs) so as to gather a set of potentially interesting candidate ESTs which were then evaluated in the context of multiple alignment with the full known TNF ligand superfamily.

XXIII. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request filed during the oral proceedings.

XXIV. The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

Acceleration of Proceedings - the National Court's Request

1. Although less frequent than acceleration requests from parties, such requests from national courts are possible (see the "Notice from the Vice-President Directorate-General 3 dated 17 March 2008 concerning accelerated processing before the boards of appeal" at OJ EPO 2008, 220 - hereafter "the Notice").

2. In the present case, the practical and economic reasons behind the national court's acceleration request were clear. The board's decision would affect the patent for all its designated states. On the one hand, if that decision should be to dismiss the appeal, with the

effect that the opposition division's decision to revoke the patent was upheld, the appeal in the national proceedings would become redundant. The saving of court time - five days according to the national court's judgment of 23 February 2009 (see *Eli Lilly and Company v. Human Genome Sciences, Inc.* [2008] EWCA Civ 168, paragraph 12) - would be significant. Further, the saving of costs by the parties if one of the two pending appeals should prove to be unnecessary would be substantial. On the other hand if, as has in fact proved to be the case, the board should allow the appeal then, not least because the parties have raised all the relevant issues in both the national and European appeal proceedings, it should assist them to have a final decision for states unaffected by the national proceedings before the appeal in those proceedings is prosecuted further.

3. The board agrees entirely with the national appeal court that parties to such parallel proceedings should inform both tribunals of the position as early as possible and ask the appropriate tribunal for acceleration in order to avoid duplication of proceedings (see *Eli Lilly and Company v. Human Genome Sciences, Inc.* [2008] EWCA Civ 168, in particular paragraphs 1 and 13). Whether acceleration is requested by one party, or both or all parties in agreement, or by a national court, all parties must accept a strict procedural framework including short time limits (see the Notice, final paragraph). It must also be understood that acceleration can have no effect on the equal treatment of all parties and cannot confer any advantage on any one party.

4. In the present case, as a result of the national appeal court's further inquiries of the board and its postponement of its own hearing until December 2009 (see Section XI *supra*), the objective of the acceleration request was achieved and the appeal proceedings were concluded considerably more swiftly than is usual, which would not have been possible without the co-operation between the national court and the board.

Main request
Article 123(2) and (3) EPC

5. The respondent raised no objections under Article 123(2) EPC to the amended claims at issue. Nor does the board see a reason to raise any of its own.

6. The respondent objected under Article 123(3) EPC to claim 13 because in its view the omission of the expression "Neutrokine-α portion" causes an extension of the scope of protection (cf. Section XXII *supra*). In the board's view, the expression "*Neutrokine-α portion*" in granted claim 20 (corresponding to claim 13 at issue) emphasised that the claimed antibody bound to the Neutrokine-α segment of any chimeric polypeptide encoded by the claimed nucleic acid molecule (cf. granted claim 1 to 8) and thereby excluded antibodies binding to known fusion partners of Neutrokine-α, which for manifest reasons could be found to lack novelty. In this respect, the board cannot accept the respondent's view that, because of its formulation, claim 20 necessarily referred only to portions (fragments) of Neutrokine-α. In referring *inter alia* back to claims 1(a) through 1(f), claim 20 points to the

polynucleotide sequences that encode the Neutrokine-α polypeptide. Claim 1, however, indicates that these are part of a nucleic acid molecule which "comprises" them, a wording which does not exclude chimeric proteins. This is reinforced by the further reference in granted claim 20 to a Neutrokine-α polypeptide of claim 15, which is a polypeptide encoded by a nucleic acid molecule of claims 1 to 8. These claims encompass polynucleotides (including fusion polypeptides) encoding the full-length amino acid sequence of the Neutrokine-α polypeptide, including the transmembrane and cytoplasmic domains. It is further noted that the patent specification makes a clear distinction between chimeric polypeptides resulting from the fusion of Neutrokine-α with known proteins (cf. *inter alia* paragraphs [0070] and [0101] of the patent-in-suit), and the epitope-bearing portions of the Neutrokine-α polypeptide itself ("*antigenic epitopes*") (cf. *inter alia* in paragraphs [0096] to [0100]).

7. As claim 13 now at issue refers directly to an antibody that specifically binds either to the full-length Neutrokine-α or to its extracellular domain, the omission of the expression "Neutrokine-α portion" is fully justified and perfectly in line with granted claim 20. There is no extension in the scope of protection in comparison with claim 20 as granted. Thus, the requirements of Article 123(3) EPC are met.

Article 84 EPC

8. Claim 6 is an independent claim directed to a recombinant vector which contains "*an isolated nucleic molecule consisting of [...]*". This latter feature

corresponds exactly to the subject-matter of claim 1 except that the term "*comprising*" has been changed to read "*consisting*". The meaning of the qualifying term "*isolated*" is clearly indicated in the patent-in-suit: "*a nucleic acid molecule, DNA or RNA, which has been removed from its native environment*" (cf. paragraph [0044]). The fact that in the same paragraph it is stated that "*recombinant DNA molecules contained in a vector are considered isolated*" is immaterial and does not create any ambiguity. The skilled reader understands perfectly well that, while claim 1 refers to a nucleic acid molecule removed from its native environment which - due to the term "*comprising*" - might contain sequences additional to the polynucleotide sequence encoding Neutrokine-α, claim 6 concerns a recombinant vector which together with all other component parts "*contains*" a polynucleotide sequence encoding Neutrokine-α removed from its native environment which - due to the term "*consisting*" - does not contain additional sequences. Thus, no clarity issue exists.

9. The respondent raised no other objections under Article 84 EPC and the board sees no reason to raise any of its own. The requirements of Article 84 EPC are fulfilled.

Article 54 EPC

10. Documents D22 and D24 have been cited by the respondent as novelty-destroying documents. They disclose the nucleic acid sequences of clones 129696 (GenBank Accession R16882) and 115371 (GenBank Accession T87299) of the IMAGE Consortium at the Lawrence Livermore

National Laboratory in Livermore, California. It is undisputed that the IMAGE clones were freely available to researchers anywhere in the world and Invitrogen Corporation was a known distributor of them. The two documents in question report partial EST sequences of human origin which are completely uncharacterised und not annotated. Evidence on file (cf. documents D48 and D50) comparing these partial sequences with the Neutrokine-α sequence of the patent-in-suit (SEQ ID NO:1) as well as the putative amino acid sequences encoded by these clones and that of Neutrokine-α (SEQ ID NO:2) shows that clone 129696 encodes amino acid residues 208 to 285 of SEQ ID NO:2 and that clone 115371 encodes amino acid residues 211 to 285 of SEQ ID NO:2. However, the nucleic acid sequence of these clones have several undetermined nucleotides and nucleotides different from those reported for Neutrokine-α, as well as sequence frameshifts when compared to the nucleic acid sequence of Neutrokine-α. Thus, the sequences of the IMAGE clones actually given in documents D22 or D24 do not anticipate the claimed subject-matter.

11. Nevertheless, the respondent relied on the declaration of Dr Kikly D84 who, thinking that the said clones actually contained more cDNA sequence than is represented in the documents, ordered the two clones from Invitrogen Corporation and sequenced them. She reports that the longest open reading frame (out of six possible ORFs) of clones 129696 and 115371 actually encodes residues 68 to 285 (i.e. over 75% of the full-length Neutrokine-α polypeptide) and 59 to 285 of SEQ ID NO:2 (100% of the extracellular domain of Neutrokine-α) respectively. Based on these findings and

with reference to decision G 1/92 (*supra*), the respondent argued that the IMAGE clones themselves anticipated the claimed subject-matter because they were commercially available, they could therefore be analysed and their analysis would have shown that they contained a nucleic acid molecule which comprised a polynucleotide sequence encoding the same residues 73 to 285 of SEQ ID NO:2, i.e. the extracellular domain of the Neutrokine-α polypeptide (cf. Section XXII *supra*).

12. The board, however, does not consider the clones of the IMAGE Consortium to have made "available to the public" in the sense of decision G 1/92 (*supra*) the subject-matter in question. Whereas the product referred to in that decision was a commercially accessible and reproducible product that had been "made available to the public" by a particular prior art use (the purpose thereof being thus fully known), the clones of the IMAGE Consortium of documents D22 and D24 were two clones with no assigned role which were physically present in a collection of about 540,000 clones and were available therefrom. The respondent retrieved them by using the knowledge of the Neutrokine-α sequence of the patent-in-suit in its search query. As a matter of fact, documents D22 and D24 contain no information whatsoever that could have drawn the skilled person's attention to them as clones possibly related to a member of the human TNF superfamily and thus motivate him/her to investigate them among all the available clones of the IMAGE collection. Although, as argued by the respondent, these two IMAGE clones were assigned specific identification numbers which showed that they were physically individualized and could be ordered and

analysed by anyone who so wished, there was nothing in the art that could have led the skilled person in a straightforward manner to these identification numbers and thereby to retrieve the corresponding IMAGE clones. The two specific clones were accessible to the public only as an **integral** part of the complete clone collection of the IMAGE Consortium. Thus, no comparison is possible with the situation underlying the rationale of G 1/92 (*supra*).

13. Whereas the location of an indexed book in a library hints at the contents of that book and thereby allows its retrieval by interrogation of that library through a direct mental procedure (cf. T 301/87, *supra*), the position of an IMAGE clone in a particular well on a specific plate, i.e. the identification number of an IMAGE clone, does not provide any indexed information on the nature or the properties of that clone so as to render it accessible to the public by a similar interrogation. Under these circumstances, their mere existence in a large collection of clones can by no means be seen as a form of implicit disclosure of anything falling under the scope of the present claims.

14. In the board's view, this conclusion is in line with the normal practice of the EPO to consider the deposition of a strain or a plasmid that contains a recombinant sequence as disclosing only the whole strain or plasmid ***in toto*** but not the details or component parts within these entities, i.e. the recombinant sequence. The specific recombinant sequence as such, "*the elements which are recognised as essential later on*", is not made available and directly

disclosed by the mere deposition of a strain or plasmid containing that sequence (cf. T 301/87, *supra*).

15. Thus, the claimed subject-matter is considered to fulfil the requirements of Article 54 EPC.

The disclosure of the patent-in-suit

16. The core issue of the present case was the evaluation of the disclosure of the patent-in-suit as seen from the point of view of Article 83 EPC (i.e. the requirement to provide a sufficiently clear and complete description of the claimed invention), Article 57 EPC (i.e. the requirement to indicate the way in which the claimed invention is industrially applicable) and Article 56 EPC (i.e. the requirement to show the non-obvious contribution to the art of the claimed invention). As pointed out in T 898/05 of 7 July 2006 (cf. point 6 of the Reasons), these three provisions of the EPC reflect from different perspectives the basic principle of the patent system that exclusive rights can only be granted in exchange for **a full disclosure** of the invention.

17. As for the principles underlying the analysis of the compliance with these requirements, there was an essential agreement between the parties and with the board on the guidance provided by the established case law of the Boards of Appeal. In particular, the recent case law on industrial applicability (cf. *inter alia* T 898/05, *supra*) has provided some criteria which both parties considered to be fully acceptable. Disagreement between the parties was not on the principles to be applied, but rather on whether or not the facts of the

present case are similar to those of a particular decision or another, which should then be followed. However, as both parties agreed that the question whether a full disclosure is provided has to be decided on a case-by-case basis depending on the technical circumstances, it is not considered necessary to analyse whether the present case is similar or not to any earlier case, but rather to carry out the analysis on the basis of the general principles, as to which there was a broad consensus.

Article 83 EPC

18. The close inter-relationship between Articles 83 and 57 EPC has been addressed in previous decisions (cf. *inter alia* T 898/05, *supra*, point 6 of the Reasons). Both provisions relate to the obligation on an applicant to give a sufficient description of the invention. As a matter of fact, in the present case, many of the objections raised under Article 83 EPC relate to Article 57 EPC as well, in particular those raised against pharmaceutical and diagnostic compositions (claims 18 and 19) as well as against anti-Neutrokine-α antibodies (claim 13) and their use in these compositions (cf. Section XXII *supra*). The relevance of these objections can only be rightly assessed in the light of the conclusions reached with regard to Article 57 EPC (*infra*). The key question here is in fact whether the patent specification discloses in sufficient terms the nature of Neutrokine-α, its purpose and how it can be used in industrial practice to solve a given technical problem.

19. Looking first at the practical aspect of reproducibility, it is undisputed that the disclosure of the nucleic acid and amino acid sequences of Neutrokine-α allows a skilled person to make all claimed embodiments without undue burden or inventive skill. The production of antibodies against a protein of known amino acid sequence does not in itself require any particular effort. These antibodies may find application in standard methods for purifying and isolating (large amounts of) the corresponding (recombinant) protein, for *in vitro* detection and/or marking that protein, etc. Whereas the use of antibodies in the preparation of pharmaceutical or diagnostic compositions may imply the identification of a condition or disease wherein that protein is involved (which is also true for the compositions themselves), the screening and selection of antibodies that may be *prima facie* of relevance for the treatment and/or detection of that condition or disease does not pose any actual technical problem since (activity) assays related to, or associated with, that condition or disease may readily be available to the skilled person, even though other criteria, such as (low) immunogenicity, (high) specificity and pharmaceutical suitability may be required for a later selection of the most appropriate antibodies.

20. As outlined below in relation to the issue of industrial applicability of the teachings of the invention, the board believes that the plausibility of the overall disclosure in relation to the prospects of a real possibility of exploitation in the pharmaceutical and/or diagnostic fields has positive reflections also on the evaluation of the sufficiency

of disclosure of the claimed invention. The claimed subject-matter is thus considered to fulfil the requirements of Article 83 EPC.

Article 57 EPC

21. Both parties agreed, as does the board, that on the basis of its structural properties, Neutrokine-α has been correctly identified in the patent-in-suit as a new member of the TNF ligand superfamily. No reasons have been put forward to dispute this conclusion. A large body of post-published evidence on file supports this finding. The question arises under Article 57 EPC whether this in itself suffices to suggest a practical way to exploit the claimed invention which is centred on Neutrokine-α, thereby providing an "*immediate concrete benefit*" (cf. T 898/05, *supra*).

22. As pointed out in T 870/04 of 11 May 2005 (cf. in particular points 5 and 6 of the Reasons), in many cases the allocation of a newly found protein to a known protein family with known activities suffices to assign a specific function to the protein because normally the members of the family share a specific function. This may be a well-characterized and perfectly understood function which provides in a straightforward manner enough support for industrial applicability. In such cases, the "*immediate concrete benefit*" is manifest. In other cases, where the members of a protein family have different, pleiotropic effects which may even be opposite and neither completely characterized nor understood, no effect can be assigned to a new member without relying on some experimental data. Between these two extreme situations, a variety

of other situations may arise for which a detailed examination of all the facts may be required. Indeed, this is the case for the TNF ligand superfamily.

23. As known in the art and acknowledged in the patent-in-suit, all members of the TNF ligand superfamily are known to participate in the regulation of (immune) cell proliferation, activation, and differentiation, and are involved in various medical conditions. They are pleiotropic cytokines which display a wide range of activities and have distinctive, but also overlapping biological functions (cf. *inter alia* paragraphs [0003] and [0004]). As acknowledged in the art, a feature common to all members (without exception) of the TNF ligand superfamily is the expression on activated T-cells and the ability to co-stimulate T-cell proliferation (cf. *inter alia* page 3381, right-hand column, lines 1 to 10, page 3382, left-hand column, lines 3 to 5 and page 3385, Table 4 of document D1; page 144, left-hand column, lines 1 to 7, page 146, right-hand column, lines 7 to 12 and page 153, sentence bridging left and right-hand columns of document D31). In view of the assignment of Neutrokine-α to the family, the skilled person expects it to display this common feature, the relevant question here being whether anything in the patent specification contradicts this expectation.

24. The patent specification, besides providing the undisputed structural identification of Neutrokine-α as a member of the TNF ligand superfamily, also provides some further relevant technical data which are fully in line with the expected properties of a member of that superfamily. In particular, it discloses the tissue

distribution of Neutrokine-α mRNA expression using the nucleic acid sequence encoding the Neutrokine-α protein (SEQ ID NO:1) as a cDNA probe and, as expected, reports - although without concrete experimental data - the expression of Neutrokine-α in activated T-cells (cf. paragraph [0032] and Example 4). It further states that "*(l)ike other members of TNF family, Neutrokine-α exhibits activity on leukocytes including for example monocytes, lymphocytes and neutrophils. For this reason Neutrokine-α is active in directing the proliferation, differentiation and migration of these cell types*" (cf. paragraph [0063]). This broad statement, far from contradicting the ability of Neutrokine-α to co-stimulate T-cell proliferation, actually supports it. In the light of the common general knowledge of the TNF ligand superfamily and its properties, no serious doubts can be cast on this explicit additional information. Nor can this information be taken as a mere theoretical or purely hypothetical assumption. First of all, it is plausible and, secondly, there is ample post-published evidence on file confirming both the presence of Neutrokine-α on activated T-cells and its ability to co-stimulate T-cell proliferation (cf. *inter alia* Tables 1 and 2 of the second declaration of Dr Kelsoe III, D175).

25. The respondent has nevertheless argued that, in view of the numerous contradictory statements and of the broad range of conditions and diseases referred to in the patent-in-suit, the skilled person would have disregarded such information as constituting only hypothetical assumptions, or speculations with no actual significant relevance (cf. Section XXII *supra*).

26. The board cannot agree with this view. When reading the patent specification, a skilled person would distinguish the positive technical information such as that mentioned above from other allegedly contradictory and broad statements found in the patent-in-suit, such as - in the respondent's view - the wide range of activities and conditions for which Neutrokine-α could be useful. This is because the skilled person realises that the description of the structure of Neutrokine-α, its structural assignment to the family of TNF ligands, and the reports about its tissue distribution and activity on leukocytes, are the first essential steps at the onset of research work on the newly found TNF ligand superfamily member. In view of the known broad range of possible activities of such a molecule, the skilled person is aware of the fact that the full elucidation of all properties requires further investigations which will gradually reveal them. In this context, the skilled person regards the long listing of possible actions of Neutrokine-α and of medical conditions in which it might take part as the enumeration or generalisation of the properties of the members of the TNF ligand superfamily. This is seen as the frame in which the newly found molecule has to be placed as one could *prima facie* have a reasonable expectation that most of them could in fact be present. At any rate, none of these specific conditions and/or activities is actually claimed and the language used in the specification is in many instances quite prudent (cf. for example in paragraph [0123] "Since Neutrokine-α belongs to the TNF superfamily, it also **should** also [sic] modulate angiogenesis" (emphasis added)).

27. Filing patents with such long lists of conditions and activities and subsequently relying on the few which have been confirmed or demonstrated is what the respondent criticised as a "boiler-plate" and "cherry-picking" practice. It can certainly be argued whether or not such a practice is proper but it is significant that the respondent acknowledged, albeit in the form of criticism of the appellant, that it is a practice used by patentees, and the appellant pointed to document D150 (the respondent's own US patent no 7,317,089, column 7, lines 24 to 40). Thus, the skilled person is acquainted with this practice and able to differentiate mere "boiler-plate" from positive technical information. In the present case, the description of the patent delivers sufficient technical information, namely the effect of Neutrokine-α on T-cells and the tissue distribution of Neutrokine-α mRNA, to satisfy the requirement of disclosing the nature and purpose of the invention and how it can be used in industrial practice.

28. As regards the effect on T-cells, the respondent argued that, in view of the technical difficulties involved in measuring the co-stimulation of T-cells by Neutrokine-α and in the absence of any detailed experimental information on the activities of Neutrokine-α listed in the patent-in-suit, the skilled person would not have been able to reproduce them without the undue burden of undertaking a research programme. Moreover, in its view, no industrial application can be directly derived from a mere co-stimulation of T-cells (cf. Section XXII *supra*).

29. The board cannot accept this line of argument. Firstly, in the light of the great number of documents concerned with known members of the TNF ligand superfamily which - as explicitly acknowledged in the patent-in-suit (cf. *inter alia* paragraphs [0006] and [0063]) - disclose standard assays for measuring their activities and effects on (immune) cells, no particular effort would be required to verify the co-stimulation of T-cells by Neutrokine-α. Even though a few contradictory results are reported in post-published documents on file (cf. *inter alia* document D3), there is also a convincing body of post-published evidence showing that, using standard assays, Neutrokine-α activity is indeed present on T-cells, in particular on mature T-cells at all stages of differentiation (cf. *inter alia* document D140 and Table 2 of the second declaration of Dr Kelsoe III, D175). Secondly, the reference in the patent-in-suit to the presence of Neutrokine-α activity in lymphocytes would inevitably prompt the skilled person to look for that activity in all types of lymphocytes, not only in T-lymphocytes but also in B-lymphocytes. There is post-published evidence on file showing that Neutrokine-α activity in B-lymphocytes could be easily measured with standard assays (cf. *inter alia* page 260, right-hand column, last five lines from the bottom to page 261, left-hand column, first paragraph of document D3). Thirdly, and contrary to the respondent's view, these activities of Neutrokine-α may represent a valid basis for a possible industrial application. In particular, the inhibition of co-stimulation and/or proliferation of lymphocytes might be *prima facie* of relevance for certain immune diseases (cf. *inter alia* paragraphs [0028] and [0108]).

30. In the board's judgment, the tissue distribution of Neutrokine-α mRNA disclosed in the patent-in-suit, in particular the expression of Neutrokine-α mRNA in B-cell and T-cell lymphomas (cf. paragraph [0032]), provides in itself in the context of the disclosure a valid basis for an industrial application. The presence of Neutrokine-α in these lymphomas, which is also confirmed by post-published evidence on file (cf. *inter alia* document D126), may be used to develop appropriate means and methods for their diagnosis and treatment based on the disclosure of the patent-in-suit.

31. The respondent, relying on alleged technical problems, argued that no industrial application could be derived from that information. In particular, reference was made to the absence of any quantitative information on the level of Neutrokine-α mRNA expression, the absence of any evidence showing the presence of Neutrokine-α on the surface of lymphoma cells, a lack of specificity arising from high levels of Neutrokine-α expression and presence in other non-cancerous tissues and the associated side-effects, the difficulties in producing therapeutic and neutralizing antibodies as well as the presence of several biologically relevant products derived from Neutrokine-α which are different from the claimed full-length Neutrokine-α and its extracellular domain (cf. Section XXII *supra*).

32. Most of these allegations are more related to Article 83 EPC than to Article 57 EPC, the relationship between the two EPC provisions having been mentioned above (cf. point 18 *supra*). In respect of Article 83 EPC, established case law of the Boards of

Appeal states that a patent may only be objected to for lack of sufficiency of disclosure if there are serious doubts, substantiated by verifiable facts (cf. T 19/90, OJ EPO 1990, 476). It would not be justified and unfair to set a different standard of proof in respect of Article 57 EPC.

33. None of the respondent's allegations has been substantiated by verifiable facts and thus, in the board's view, they must be seen as unsupported assumptions. All the more so since the claims are commensurate with the level of the disclosure and are not directed to specific optimised (antibodies) products or related to specific optimised (diagnostic or therapeutic) assay conditions. Moreover, post-published evidence on file shows the production of anti-Neutrokine-α antibodies and their possible application for therapy and diagnosis purposes, confirming the plausibility of the disclosure of the patent-in-suit (cf. *inter alia* page 4543, left-hand column, last paragraph and Fig. 2A of document D126, and document D173).

34. Thus, in line with the principles developed in the case law of the Boards of Appeal, the board finds the patent-in-suit provides a concrete technical basis for the skilled person to recognise a practical exploitation of the claimed invention in industry. Thus, the requirements of Article 57 EPC are fulfilled.

Article 56 EPC

Document D1 as closest prior art

35. In the board's view, the most appropriate starting point for the evaluation of inventive activity is represented by a review document of the TNF ligand superfamily. There are on file at least two such documents, namely D1 and D31, both from the research group of H-J. Gruss. D1 discloses nine members of the superfamily, while D31 discloses an additional one (cf. Table 1, page 3381 of document D1 and Table 1, page 146 of document D31).

36. Starting from that prior art, the underlying technical problem of the present case is seen as being the provision of a further member of the TNF ligand superfamily. The formulation of the problem *per se* does not involve in itself any inventive merit since it manifestly derives from the prior art. As concluded above in relation to Articles 83 and 57 EPC, the patent specification convincingly discloses the finding of Neutrokine-α as a new member of the TNF ligand superfamily and thus provides in the claims at issue a solution to the underlying technical problem. The question remains whether such a solution was obvious or not to the skilled person.

37. Methods and means to identify new members of the TNF ligand superfamily were known to the skilled person. In particular, members of that superfamily were known to have C-terminal (extracellular) domains with a significant homology and a characteristic pattern of sequence conservation. Nine short regions have conserved sequences which map to the strands forming

the ß-pleated sheets of the protein (ß-jellyroll) and wherein the centrally located D-strand has the greatest conservation (cf. *inter alia* page 3380, paragraph bridging left and right-columns, page 3384, Figure 2 in document D1, paragraph bridging pages 676 and 677 in document D32). Based on these conserved regions, EST databases had already been searched for new members of the TNF ligand superfamily (cf. *inter alia* page 152, right-hand column, last paragraph in document D31 and paragraph bridging pages 673 and 674, page 679, left-hand column, second full paragraph to right-hand column, first paragraph in document D32). Thus, the route for searching for new members was known and it was obvious to the skilled person to embark on such a search. Was it then reasonable to expect the finding of Neutrokine-α through that route?

38. There is evidence on file showing that the use of the full-length sequence of the members of the TNF ligand superfamily known at the filing date, fragments of their conserved C-terminal domains or the most conserved D-strand, failed to detect any EST sequence encoding Neutrokine-α, such as those of documents D2, D22 and D24 (cf. *inter alia* the declaration of Dr Farrow D75). Indeed, document D32, using the D-strand for querying EST databases, reports the isolation of a single EST (TRAIL) only and fails to identify any EST sequence encoding Neutrokine-α. Post-published documents disclosing the Neutrokine-α sequence refer to very particular means used for the search: a) In document D10 "*an improved profile search*" is used for screening public databases (cf. page 1750, left-hand column, first full paragraph); b) document D25 refers to the production of a particular human cDNA "*data base*

containing more than 2 million ESTs obtained from over 750 different cDNA libraries" (cf. page 15978, right-hand column, second full paragraph); and c) document D3 also mentions a particular human neutrophil-monocyte-derived cDNA library (cf. page 260, left-hand column, first paragraph).

39. In the light thereof, the board concludes that the skilled person had no reasonable expectation of finding the Neutrokine-α sequence by following the route indicated in the prior art.

Document D2 as closest prior art

40. The board agrees with the respondent in that every EST clone of a public EST database (EMBL/GenBank/DDBJ) is part of the state of the art and available to the skilled person (cf. Section XXII *supra*). However, contrary to the respondent's arguments, the board does not see how each and every EST clone of the database can be considered to be an equally valid starting point for the assessment of inventive step. The EST clone of document D2, which is uncharacterised and not annotated, cannot be singled out from all the other EST clones present in the public EST database without an objective compelling reason for making such a selection. Although being physically present in the available collection of clones, a particular EST clone is not made available as such, i.e. as a particular, individualized product, but only as an **integral** part of the whole EST database ***in toto***. In the absence of any specific information (such as the identification of its putative encoded polypeptide), the mere disclosure of a nucleic acid sequence in itself does not go beyond that disclosure

and, in the board's opinion, does not allow for its use or selection as closest prior art.

41. Apart from a specific nucleic acid sequence, there is no other information given in document D2 and thus, the selection of the EST clone of document D2 as closest prior art requires hindsight knowledge of the patent-in-suit.

Document D34 as closest prior art

42. Undisputed evidence on file shows that the nucleic acid sequence of the EST clone of document D34 (IMAGE clone 450662) was not publicly available before the filing date of the patent-in-suit (cf. declaration of Dr Cash D52). The fact that the IMAGE clone itself had been made available to Washington University in St. Louis for sequencing is irrelevant since the clone *per se* does not render the nucleic acid sequence contained in that clone immediately available to the skilled person (cf. point 14 *supra*). Also, using this clone as starting point for the assessment of inventive step would be at any rate inappropriate for the reasons already given above in respect of document D2.

Pipeline screening

43. The respondent proposed also "pipeline screening" as a way which would be envisaged by the skilled person to arrive at the claimed subject-matter, i.e. a method based essentially on an analysis of freely available, unidentified EST sequences for similarity to sequences available from a publicly available database of

annotated protein sequences using publicly available search software.

44. Whereas an automated pipeline screening might avoid the selection of a particular EST clone with the hindsight knowledge of the patent-in-suit, the screening of the complete EST sequences of a public EST database (such as those of the IMAGE Consortium) against the sequences of a public protein database (such as Swiss-Prot) would not have been performed out of idle curiosity, in view of the sheer size of these databases and the effort and resources required (*infra*), but only with a specific technical purpose or target in mind. Indeed, depending on the intended purpose, the search programs, values and parameters used to carry out the automated pipeline screening would have to be defined and selected accordingly by the skilled person. In fact, there is a difference between looking for members of a protein family which are known to have high sequence identity and looking for members of a protein family having only a low sequence identity. Again, differences might arise when sequence identity is known to be homogeneously spread across the complete sequence of the proteins or when it is only limited to a unique (highly) conserved domain.

45. Evidence for such a selection is found in document D86 which refers to the use of both BLAST and FASTA, the latter used for searching copies of specific (spliced-leader) sequences (cf. page 124, right-hand column, first full paragraph, page 126, footnote of Table 1 and right-hand column, first full paragraph). Evidence is also on file showing that FASTX and BLASTX were also available to the skilled person at the filing

date of the patent-in-suit and that the results obtained might be different depending on the search program used and on the parameters and values selected for running those programs.

46. In the view of the respondent (cf. Section XXII *supra*), document D86 shows that automated pipeline screening of EST clones of a cDNA library was a standard method at the filing date of the patent-in-suit performed by the skilled person with no purpose in mind other than the broad determination of putative encoded proteins. It is noted, however, that the method disclosed in document D86 does not use all the EST clones of the cDNA library described in that document but, as a first step, refers to a random selection of EST clones that significantly reduces the number of distinct clones and EST sequences to analyze (585 clones generating 720 EST sequences). That number is much lower by far than that of the EST sequences present in public EST databases (GenBank, EMBL, IMAGE Consortium) available to the skilled person at the filing date of the patent-in-suit. The sheer number of EST sequences in these public databases (hundreds of thousands) renders any comparison of time, effort and resources completely inappropriate.

47. Indeed, not even the respondent appears to rely on such a broad approach. By pointing to the references in document D86 to the searches of daily updates of these public EST databases and to the pre-selection of sequences to remove high copy number cDNAs (cf. page 124, left-hand column, last paragraph and page 130, left-hand column, last paragraph), as well as to other possible criteria (such as the removal of EST sequences encoding proteins of known and/or highly present

protein families), the respondent acknowledges that an appropriate starting point for an automated pipeline screening would not be the complete EST sequences of a public EST database but a particular selection of these sequences.

48. In view of the large number and particular nature of possible criteria that may be used to carry out the selection of those EST sequences as well as the programs, parameters and values that should have to be selected accordingly, the board comes to the conclusion that no particular prior art, i.e. no particular group of EST sequences, has been clearly and unambiguously identified as a starting point for an automated pipeline screening nor has a document been clearly identified as representing that closest prior art. Moreover, there is no evidence on file demonstrating with certainty that each and every one of the suggested selections, or at least most of them, would have contained at least one EST sequence encoding (part of) the Neutrokine-α sequence of the patent-in-suit, such as those shown in documents D2, D22 or D24, and that with an automated pipeline screening the skilled person would have been in a position to recognize that sequence immediately and successfully retrieve it. Thus, in the board's judgment, the pipeline approach is untenable.

Conclusion

49. For the above reasons, the board concludes that the claimed subject-matter fulfils the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of claims 1 to 19 of the main request filed during the oral proceedings and a description and figures to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski L. Galligani