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D E C I S I O N
of 7 July 2006

Case Number: T 0898/05 - 3.3.08

Application Number: 97924775.6

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Title of invention:
Hematopoietic cytokine receptor

Applicant:
ZymoGenetics, Inc.

Opponent:
-

Headword:
Hematopoietic receptor/ZYMOGENETICS

Relevant legal provisions:
EPC Art. 52(1), 57
EPC R. 23(b)(1), 23e(3), 27(1)(f)

Keyword:
"Main request - industrial application (yes)"
"Referral to the Enlarged Board of Appeal (no)"
"Remittal to the first instance (yes)"

Decisions cited:
T 0144/83, T 0338/00, T 0604/04, T 0870/04

Catchword:

1. For the purposes of Article 57 EPC, a claimed invention must have such a sound and concrete technical basis that the skilled person can recognise that its contribution to the art could lead to practical exploitation in industry, i.e. to a

concrete benefit, which is immediately derivable directly from the description, if it is not already obvious from the nature of the invention or from the background art. It is necessary to disclose in definite technical terms the purpose of the invention and how it can be used in industrial practice to solve a given technical problem, this being the actual concrete benefit or advantage of exploiting the invention. (cf. points 5 and 6 of the Reasons).

2. The fact that a function is based on computer-assisted methods, rather than on the basis of traditional wet-lab techniques, does not mean that it has to be automatically disregarded or excluded from a careful and critical examination. Their probative value has to be examined on a case-by-case basis regarding the nature of the invention and the prior art relating thereto (cf. point 22 of the Reasons).

3. The function of a protein (and thus of the nucleic acid encoding it) can be seen at different levels, which include its molecular function, its cellular function and its biological function in a broad sense. The elucidation of one of these particular levels of function might result, under certain conditions, in a straightforward industrial application, even though the other levels of activity remain completely unknown or only partially characterized. For the purpose of Article 57 EPC and Rules 23e(3) and 27(1)(f) EPC, none of these levels is more fundamental than the other ones insofar as at least from one of these levels a practical application (a profitable use in a wider sense) is derivable in a straightforward manner (cf. points 29 and 30 of the Reasons).



Case Number: T 0898/05 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 7 July 2006

Appellant: ZymoGenetics, Inc.
1201 Eastlake Avenue East
Seattle, WA 98102 (US)

Representative: Bizley, Richard Edward
HLBBshaw
Merlin House
Falconry Court
Baker's Lane
Epping, Essex CM16 5DQ (GB)

Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 23 February 2005
refusing European application No. 97924775.6
pursuant to Article 97(1) EPC.

Composition of the Board:

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

Summary of Facts and Submissions

- I. The applicant (appellant) lodged an appeal against the decision of the examining division dated 23 February 2005 whereby the European patent application No. 97 924 775.6, which originated from an international application published as WO 97/44455, was refused pursuant to Article 97(1) EPC.
- II. The decision under appeal was based on a main request and an auxiliary request filed with the applicant's letter of 16 February 2004. Both requests were found by the examining division to contravene Article 57 EPC and Rule 23e(3) EPC.
- III. On 28 June 2005, the appellant filed a statement of grounds of appeal wherein the requests before the examining division were maintained and re-filed. The examining division did not rectify its decision and remitted the appeal to the board of appeal under Article 109(2) EPC.
- IV. With the statement of grounds of appeal, the appellant also requested oral proceedings if the board was not prepared to grant a patent on the basis of the main request. After a telephone consultation with the board's rapporteur on 23 February 2006, wherein the appellant's representative was informed of the preliminary positive opinion of the board on Article 57 EPC and of its intention to remit the case to the first instance, the appellant's representative, in its letter of 2 March 2006, withdrew the request for oral proceedings if the board should find the application met the requirements of Article 57 EPC and Rule 23 EPC.

V. The **main request** comprised 15 claims, wherein independent claims 1, 9, 11, 12 and 15 read as follows:

"1. An isolated polynucleotide, optionally DNA, encoding a ligand-binding receptor polypeptide, said polypeptide comprising a sequence of amino acids selected from the group consisting of:

- (a) residues 33 to 235 of SEQ ID NO: 3; and
- (b) residues 25 to 229 of SEQ ID NO: 7."

"9. An isolated polypeptide comprising a segment selected from the group consisting of:

- (a) residues 33 to 235 of SEQ ID NO: 3; and
- (b) residues 25 to 229 of SEQ ID NO: 7,

wherein said polypeptide is substantially free of transmembrane and intracellular domains ordinarily associated with hematopoietic receptors;

optionally said polypeptide further comprising an affinity tag, e.g. polyhistidine, protein A, glutathione S transferase, substance P, maltose binding protein, or an immunoglobulin Fc polypeptide."

"11. A chimeric polypeptide consisting of a first portion and a second portion joined by a peptide bond, said first portion consisting essentially of a ligand binding domain selected from the group consisting of:

- (a) residues 33 to 514 of SEQ ID NO: 3; and
- (b) residues 25 to 508 of SEQ ID NO: 7,

and said second portion consisting essentially of an affinity tag, e.g. an immunoglobulin Fc polypeptide."

"12. A method for detecting a ligand within a test sample, comprising contacting a test sample with a polypeptide, optionally immobilized on a solid support, said polypeptide comprising a segment selected from the group consisting of:

- (a) residues 33 to 235 of SEQ ID NO: 3; and
- (b) residues 25 to 229 of SEQ ID NO: 7, and detecting binding of said polypeptide to ligand in the sample."

"15. An antibody that specifically binds to either:

- (a) residues 33-514 of SEQ ID NO: 3; or
- (b) residues 25-508 of SEQ ID NO: 7."

Claims 2 to 5 concerned particular embodiments of claim 1 and defined the presence of further elements in the ligand-binding receptor polypeptide (a fibronectin type III domain, a transmembrane domain, an intracellular domain and an affinity tag, etc.). Claims 6 and 7 concerned expression vectors comprising several elements (transcription promoter and terminator) including a DNA segment encoding a secretory peptide and a ligand-binding receptor polypeptide of claims 1 to 5. Claim 8 referred to a cultured cell into which an expression vector according to any one of claims 6 to 7 had been introduced. Claim 10 was directed to the polypeptide of claim 9 immobilized on a solid support. Claims 13 and 14 concerned particular embodiments of the method of claim 12.

VI. The following documents are cited in the present decision:

D2: Q. Chen et al., *Nature*, 19 October 2000, Vol. 407, pages 916 to 920;

D3: H. Yoshida et al., *Immunity*, October 2001, Vol. 15, pages 569 to 578;

D5: S. Pflanz et al., *Immunity*, June 2002, Vol. 16, pages 779 to 790;

D7: C. Schmidt et al., *Inflamm. Bowel Dis.*, January 2005, Vol. 11(1), pages 16 to 23.

VII. The reasons given by the examining division in the decision under appeal may be summarised as follows:

Although it was credible, based on sequence homology, that the Zcytor1 protein disclosed in the application could belong to the cytokine receptors subfamily of IL-6, IL-11, G-CSF, CNTF, OSM, CT-1 and leukemia inhibitory factor (LIF) receptors, a specific function could not be derived from the structural data provided in the application. The claimed protein was only characterized in structural terms and in terms of localization of expression, but not in functional terms. The structural relation between the Zcytor1 and the subfamily of cytokine receptors was established by computer-assisted alignment. These studies did not allow any concrete conclusion to be drawn concerning the actual function of the protein but rather only speculations of a vague nature.

The decision under appeal stated *expressis verbis*:
"Applicant predicted that the protein Zcytor1 has a role in proliferation, differentiation and/or activation of immune cells [...] This was **reasonably credible** and has now been confirmed. However, this "function" (the parentheses are used to indicate that the so-called function indicated is not considered to be an acceptable function in the context of the consideration of industrial applicability) is so **vaguely defined** that **no specific biological function** which would implicate a therapeutic use or a diagnostic use has been defined" (emphasis added).

It was further stated that the disclosed Zcytor1 was merely a research tool important for establishing a research program, i.e. the application did not provide a complete invention but only a first step in the quest to provide industrially applicable matter. It was only at this subsequent step (not reached in the application) that the actual function of Zcytor1 could be determined. In conclusion, no actual biological role or function was demonstrated and the members of the identified subfamily of cytokine receptors obviously all had different functions. Hence, it was not at all clear which conditions could be diagnosed or treated using the protein Zcytor1 and what utility the protein or DNA could have. Since the function of Zcytor1 was not established in the application, the subject-matter of the claims did not fulfil the provisions of Article 57 EPC in combination with Rule 23(e)(3) EPC.

No conflict was seen by the examining division between Rule 23(e)(3) EPC and Article 57 EPC. In the light of this Rule, Article 57 EPC could no longer be

interpreted in the classical sense, i.e. if the protein in question could be made then the requirements of this Article were already fulfilled. The existence of Rule 23(e)(3) EPC required an examination as to whether or not the use requirement of Article 57 EPC was fulfilled, the answer in the present case being negative.

VIII. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Article 57 EPC provided two alternatives for an invention to be susceptible of industrial application, namely that it could be made or used in any kind of industry, including agriculture. Consequently, if the claimed invention could be made, it already met the requirements of the EPC as regards susceptibility of industrial application. Even if the language of Article 57 EPC were interpreted as meaning that the "making" referred to had to be in industry, there was nothing to indicate that the word "industry" had a particular or narrow meaning. In the context of this broad nature of industry, the "could be made in industry" test was more than enough for any invention. This interpretation could not to be changed by Rule 23(b)-(e) EPC since the Implementing Regulations were not to be used for changing the initial basic meaning of the EPC without infringing Article 164(2) EPC. Rule 27(1)(f) EPC did not provide any further definition beyond that derivable from Article 57 EPC itself, it only imposed an additional practical requirement in case the way in which the invention was capable of exploitation in industry was not obvious from the description or the nature of the invention.

So as not to conflict with the first option afforded by Article 57 EPC, the industrial application of a sequence or a partial sequence referred to in Rule 23e(3) EPC was satisfied merely by the explicit or implicit disclosure of the capability of making the relevant gene or sequence in any kind of industry. This was in agreement with a narrow interpretation of this Rule, otherwise it would constitute a broadened exception to patentability contrary to the normal approach of the Boards of Appeal.

The other relevant legal background that had to be taken into account was the EU Directive 98/44/EC on the legal protection of biotechnological inventions and its adoption by the EPO. Recitals (22), (28) and (34) all emphasized and made clear that the legislative intention was not to change relevant basic law, *inter alia*, the provisions on susceptibility to industrial application. Whereas in Recital (23) the patentability of a mere DNA was denied, immediately afterwards in Recital (24) it was specified that in connection with a gene sequence or partial gene sequence it was necessary to specify which protein or part of a protein was produced or what function it performed. This Recital thus asserted a choice of route whereby compliance with the industrial application criterion was achievable. If this Recital (24) was to be used, however, as requiring an indication of a use or of a function of a DNA sequence in a case where the requirements of Article 57 were satisfied merely by the capability of making the sequence in industry, then Recital (24) was in collision or conflict with the EPC since such a requirement was not derivable from Article 57 EPC

itself. However, it was not the Directive itself which was the governing law; it was the manifestation of the corresponding provisions in Rule 23(b)-(e) of the Implementing Regulations to the EPC. Thus, in case of a conflict, in accordance with Rule 23b(1) EPC, which stated that the Directive was only to be used as supplementary means of interpretation, the guidance of the Directive ceased and Rule 23(b)-(e) EPC had to be interpreted in the normal way. In any case, should there be an inconsistency between Rule 23(b)-(e) and Article 57 EPC, then it was the provisions of Article 57 EPC that governed per Article 164(2) EPC.

The use of a research tool was an appropriate basis for asserting susceptibility of industrial application in addition to (and as an alternative to) the capability of making a "gene sequence" invention in any kind of industry. There was no requirement or legal provision in either the EPC or its Implementing Regulations that an invention relating to a gene sequence should have a therapeutic or diagnostic use as such. It was also a very long-established legal principle that exceptions to patentability were to be construed narrowly. The imposition of a further or additional layer of restrictions (in the form of a therapeutic or diagnostic use) to the provisions of the Implementing Regulations, which were themselves narrower than the EPC, had no basis in law.

If the board arrived at any different interpretation and conclusion with regard to Article 57 EPC and Rule 23(b)-(e) EPC, important points of law were then involved and a referral to the Enlarged Board of Appeal was appropriate. Several questions to the Enlarged

Board of Appeal were specifically suggested for such a referral.

The application explicitly described the Zcytor1 as a cytokine receptor with a role in the proliferation, differentiation and activation of immune cells; Zcytor1 was also implicated in the development and regulation of immune responses. Specific applications based on the manipulation of the activity of the disclosed receptor were further disclosed. Whereas Zcytor1 agonists could be used in stimulating cell mediated immunity and lymphocyte proliferation, Zcytor1 antagonists could be used in the suppression of immune responses, such as in the treatment of autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, diabetes, etc. and for reducing rejection of tissue or organ transplants. Also in connection with the use of these antagonists, the application taught the expression of soluble fusion proteins of Zcytor1 with immunoglobulin heavy chain constant regions (Zcytor1/Ig), which were useful as *in vivo* antagonists.

The statements made in the application had been confirmed to be correct. Later document D5 showed that Zcytor1 (also known as WSX-1, IL-27RA or TCCR) was a receptor responsive to the cytokine ligand IL-27, an important early factor in the development of Th1 responses and suppressing Th2 responses. Soluble IL-27 receptor (IL-27RA-Ig; extracellular domain of IL-27RA fused to immunoglobulin Fc) neutralised IL-27 *in vitro* and it could modulate Th1-mediated auto- or allo-immune diseases *in vivo*. Applicant's unpublished data showed that soluble IL-27RA-Ig neutralised the biological activity of IL-27 *in vitro* and that it diminished

delayed-type hypersensitivity response *in vivo*. Other researchers had published data showing that treatment with neutralising IL-27 p28-specific antibody products protected rodents from developing EAE and rheumatoid arthritis disease. Clearly, the application disclosed specific functions and uses of the Zcytor1 receptor that were factually accurate and confirmed by post-filed data.

There was no basis in the law for requiring a function of a sequence to be "specific" or for having any form of concern about the "vagueness" of a sequence's function. The examining division adopted the position that what was not "specific" was vague and, *ipso facto*, not enough for patentability. This view ignored the law and went against basic common sense and fundamental fairness. In fact, functions upon which industrial activity could be supported were often general and not "specific" in the way the examining division meant.

- IX. The appellant (applicant) requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or, alternatively, the auxiliary request as filed with the statement of grounds of appeal (cf. Section III *supra*).

Reasons for the Decision

*Articles 52(1) and 57 EPC; Rules 23e(3) and 27(1)(f) EPC
General considerations and case law*

1. According to Article 52(1) EPC for a European patent to be granted an invention has to satisfy *inter alia* the

- requirement of being "*susceptible of industrial application*". According to Article 57 EPC, this requirement is fulfilled if the invention "*can be made or used in any kind of industry, including agriculture*". In this respect, Rule 27(1)(f) EPC prescribes that the description should "*indicate explicitly, when it is not obvious from the description or nature of the invention, the way in which the invention is capable of exploitation in industry*." Rule 23e(3) EPC, which relates to biotechnological inventions, similarly requires that "*the industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application*".
2. The case law indicates that the notion of "industry" has to be interpreted broadly so as to include all manufacturing, extracting and processing activities of enterprises that are carried out continuously, independently and for financial (commercial) gain (cf. e.g. "Case Law of the Boards of Appeal of the EPO", 4th edition 2001, I.E.1, 141 and *inter alia* T 144/83, OJ EPO 1986, 301, see point 5 of the Reasons). In decision T 870/04 of 11 May 2005, it was held that the mere fact that a substance (e.g. a polypeptide) can be made in some way does not necessarily mean that the requirements of Article 57 EPC are fulfilled, unless there is also some **profitable use** for which the substance can be employed (cf. points 3 and 4 of the Reasons).
 3. The latter decision gives some general guidance for assessing the compliance of biotechnological inventions concerned with substances found in nature (e.g. a protein, a DNA sequence, etc.) with the requirements of

Article 57 EPC. A distinction is made therein between **i)** cases where, in addition to the structure of the substance in question, its function is also elucidated or is already known from the art, and **ii)** cases where the substance is identified, and possibly also characterised, but either its function is not known or is complex and incompletely understood and there is no disease or condition attributable to an excess or deficiency of the said substance. It is stated that in cases falling under **i)** a practical industrial application of the substance in question can in general be easily seen and, if so, the requirements of Article 57 EPC are fulfilled, whilst in cases falling under **ii)** if no practical application can be envisaged, industrial applicability cannot be acknowledged (cf. points 5 and 6 of the Reasons). With reference to the second group of cases, the board indicated that *"there must be a borderline between what can be accepted, and what can only be categorized as an interesting research result which per se does not yet allow a practical industrial application to be identified"* and that *"even though research results may be a scientific achievement of considerable merit, they are not necessarily an invention which can be applied industrially"*.

4. As seen above, the case law refers to the concepts of "financial (commercial) gain" (cf. T 144/83, supra) and of "profitable use" (cf. T 870/04, supra) in relation to industrial applicability. In the board's judgement, those two expressions both tend to convey the same idea: patents being an incentive to innovation and economic success, the criterion of "industrial applicability" requires that a patent application describes its subject invention in sufficiently meaningful technical

terms that it can be expected that the exclusive rights resulting from the grant of a patent will lead to some financial or other commercial benefit.

5. The board considers that the need to show a "profitable use" is not to be understood in the narrow sense of an actual or potential economic profit (i.e. generating more income than expenditure) or of a commercial interest (i.e. creating a new or increased business opportunity). Rather, it must be understood in the wider sense that the invention claimed must have such a sound and concrete technical basis that the skilled person can recognise that its contribution to the art could lead to practical exploitation in industry. It would be at odds with the purpose of the patent system to grant exclusive rights to prevent the commercial activities of others on the basis of a purely theoretical or speculative patent application. This would amount to granting a monopoly over an unexplored technical field.

6. The board takes the view that, in the present context, the concept of "profit" should be seen in its wider sense of benefit instead of its narrower sense of financial reward. Accordingly, the expression "profitable use" should be understood more in the sense of "immediate concrete benefit". This conveys, in the words "concrete benefit", the need to disclose in definite technical terms the purpose of the invention and how it can be used in industrial practice to solve a given technical problem, this being the actual benefit or advantage of exploiting the invention. The essence of the requirement is that there must be at least a prospect of a real as opposed to a purely

theoretical possibility of exploitation. Further, the use of the word "immediate" conveys the need for this to be derivable directly from the description, if it is not already obvious from the nature of the invention or from the background art. It should not be left to the skilled reader to find out how to exploit the invention by carrying out a research programme. Not only is this the essence of the requirements of Rules 23e(3) and 27(1)(f) EPC, it also corresponds to the requirements of Articles 56 (the need to provide a non-obvious solution to a technical problem), 57 (the need to indicate how to exploit the invention), and 83 EPC (the need to provide a sufficient disclosure of the claimed invention). All those provisions reflect the basic principle of the patent system that exclusive rights can only be granted in exchange for a full disclosure of the invention.

7. Accordingly, a product whose structure is given (e.g. a nucleic acid sequence) but whose function is undetermined or obscure or only vaguely indicated might not fulfil the above criteria, in spite of the fact that the structure of the product per se can be reproduced (made) (cf. case of T 870/04, point 10 *infra*). If a patent is granted therefor, it might prevent further research in that area, and/or give the patentee unjustified control over others who are actively investigating in that area and who might eventually find actual ways to exploit it.

8. On the other hand, a product which is definitely described and plausibly shown to be usable, e.g. to cure a rare or orphan disease, might be considered to have a profitable use or concrete benefit, irrespective

of whether it is actually intended for the pursuit of any trade at all. Thus, although no particular economic profit might be expected in the development of such products, nevertheless there is no doubt that it might be considered to display immediate concrete benefits.

The case of decisions T 870/04, T 338/00 and T 604/04

9. It is considered useful at this point to see how the question of "industrial applicability" has been decided in some recent biotechnological cases.

10. In the case of decision **T 870/04** (*supra*), the board was confronted *inter alia* with a claim directed to an isolated human polypeptide designated BDP1 ("Brain Derived Phosphatase 1") which was described as having unique properties that could reflect specific functions in cellular signal transduction pathways and a possible role in cellular housekeeping and in certain types of cancer. The application did not explicitly disclose the specific nature and the possible significance of these suggested roles for BDP1. The board found that the application stopped short of suggesting, let alone identifying for BDP1 an anti-cancer activity or a therapeutic use as a tumour-suppressor agent. Moreover, taking into account the fact that both cancer and cellular housekeeping are complex cellular processes which involve a large number of genes and/or proteins with multiple specific interconnections and finely tuned regulations, the nature and significance of these roles could not be inferred from the application itself nor from the background art. Thus, the board concluded that, although the application described a product (a polypeptide), means and methods for making it, and its

prospective use thereof for basic scientific activities, it identified no practical way of exploiting it in at least one field of industrial activity. In the board's view, the only practicable use suggested was to use what was claimed to find out more about the natural functions of what was claimed itself. This would not in itself be an industrial application, but rather research undertaken either for its own sake or with the mere hope that some useful application would be identified. The board took also into account a post-published article written by the inventors themselves and, after analysis thereof, came to the conclusion that, even eight years after the priority date of the application, a tumour suppressor activity was not yet completely evident even to the inventors.

11. In the case of **T 338/00** of 6 November 2002, the board examined whether, for the claimed heterodimeric receptor or dimer and for the claimed method to modulate transcription activation of a gene, the way in which they were capable of being exploited in industry could be derived from the description or whether what was described was merely an interesting research result that might yield a yet to be identified industrial application. The board found that the application not only disclosed the presence of cooperative interactions to form heterodimeric receptors between the retinoic acid receptor RXR and other members of the steroid/thyroid hormone receptor superfamily but provided also further evidence on the use of these heterodimers for modulating suitable transcription expression systems. There was explicit reference to the possible relevance of the heterodimers in several physiological processes. Moreover, the application made

available an *in vitro* method for screening the suitability of other members of the steroid/thyroid hormone receptor superfamily to form heterodimers with RXR and, implicitly, its possible use to screen further compounds for their ability to modulate and/or alter the disclosed cooperative interactions. In the board's judgement, such activities and products were aimed at a direct technical result that could be applied in an industrial activity. Thus, it was concluded that the requirements of Article 57 EPC were met.

12. In the case of decision **T 604/04** of 16 March 2006, the patent application provided a structural characterisation of polypeptide receptors which enabled their assignment to the category of receptors which bind members of the PF4A family of chemokines and, insofar, indicated what their function could be. Yet, there was no characterisation of their ligands, and thus this function remained at best incompletely understood. However, taking into account the common general knowledge at the filing date, the board found that chemokines as a family were considered not only to be interesting in fundamental research but also as important for the pharmaceutical industry irrespective of whether or not their role had been clearly defined. This also suggested that their receptors must have been considered equally important since the mode of action of chemokines is through them. In view of this, the board found it reasonable to conclude that the polypeptides in question, which exhibited the characteristics of receptors of members of the PF4A family of cytokines, would have been regarded as important to the pharmaceutical industry, i.e. that industrial applicability could be acknowledged.

The disclosure of the present application

13. The present application discloses the nucleotide sequence and the encoded amino acid sequence of the human transmembrane receptor Zcytor1 (SEQ ID NO.: 2 and 3) and the sequences of a natural splicing or allelic variant thereof (SEQ ID NO.: 4 and 5). The nucleotide and amino acid sequences of the corresponding Zcytor1 receptor from mouse are also disclosed in the application (SEQ ID No.: 6 and 7). Based on the general **structure** of this receptor and several specific **structural** features, which include an extracellular or ligand-binding domain with the presence of an hematopoietin conserved "TrpSerXTrpSer" (WSXWS) motif, three fibronectin III domains, a conserved "CysXTrp" (CXW) motif and the presence of Cys (C), Trp (W), Arg (R) residues at some specific positions, the Zcytor1 receptor is identified as a putative member of the hematopoietin receptor family (cf. page 5, line 22 to page 6, line 2; page 7, lines 1 to 9 and page 7, line 35 to page 9, line 18 of the application as published). This family belongs to the more general cell-surface cytokine receptor superfamily and includes among others the receptors for IL-6, IL-11, G-CSF, CNTF, OSM, CT-1 and leukemia inhibitory receptor (LIF) (cf. page 8, line 13 to page 9, line 18).
14. The application further discloses studies on the tissue distribution of the Zcytor1 expression (cf. page 29, Example 4). The analysis of these studies shows that the expression of the Zcytor1 receptor is *"widespread, with high levels of expression observed in lymphoid tissues, including thymus, spleen, lymph nodes, and*

peripheral blood leukocytes. The receptor is present on both B- and T-cells, with T-cell levels generally higher" (cf. page 7, lines 10 to 14). These data are interpreted as indicating "a role for the Zcytor1 receptor in proliferation, differentiation, and/or activation of immune cells, and suggest a role in development and regulation of immune responses", in particular "a role in early thymocyte development and immune response regulation" (cf. page 7, lines 14 to 16 and page 19, lines 30 to 33). It is also stated that "the interaction of Zcytor1 with its ligand may stimulate proliferation and development of myeloid cells and may, like IL-6, LIF, IL-11 and OSM (Baumann et al., J. Biol. Chem. 268:8414-8417, 1993), induce acute-phase protein synthesis in hepatocytes" (cf. page 7, lines 16 to 19). No further experimental evidence supports this suggested role for the Zcytor1 receptor.

15. The Zcytor1 receptor is proposed for use in different screening methods, in particular to *"screen for ligands for the receptor, including the natural ligand, as well as agonists and antagonists of the natural ligand"* (cf. page 17, lines 11 to 14). The agonist ligands are said to be useful in different **therapeutic conditions** associated with the stimulation of cell-mediated immunity and of lymphocyte proliferation, such as in the treatment of infections involving immunosuppression, etc. (cf. page 20, lines 5 to 13). Similarly, for the antagonist ligands several **therapeutic applications** are explicitly indicated, in particular for the treatment of autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, reduction of rejection of tissue or organ transplants and grafts, etc. (cf. page 20, lines

- 14 to 18). Apart from the mentioned studies on tissue distribution, there is no experimental evidence supporting these therapeutic applications for the Zcytor1 agonists and/or antagonists ligands.
16. There is no disclosure of any specific agonist ligand. However, the application explicitly refers to the production of soluble ligand-binding fragments and to the expression of a receptor extracellular domain as a fusion with immunoglobulin heavy chain constant regions, typically an F_c fragment, and their use as antagonist ligands *in vivo* (cf. *inter alia* page 20, line 30 to page 21, line 15). The production of recombinant soluble Zcytor1 and Zcytor1/IgG fusion receptors is exemplified with both the human and mouse Zcytor1 (cf. Examples 7 and 8, page 32, line 32 to page 35, line 10). Both full-length Zcytor1 receptor as well as truncated (soluble, extracellular) fragments thereof and fusion receptors are contemplated in the claim request refused by the examining division.

Post-published evidence

17. Several post-published documents were cited during the examination proceedings as well as in the appeal proceedings. Although at the time of the application the natural ligand of the Zcytor1 receptor was not yet known, documents D2 and D3 - published respectively four and five years after the priority date of the present application (23 May 1996) - identify the Zcytor1 receptor (here named T-cell cytokine receptor, TCCR and WSX-1 receptor, respectively) as a member of the class I cytokine receptor family and they confirm the role of this receptor in the regulation of the

T-cell (Th1) immune responses, in particular for the initial production of IFN- γ and induction of Th1 responses but not for its maintenance (cf. paragraphs bridging left- and right-hand columns on pages 917 and 919 of document D2; page 570, left-hand column, first paragraph, page 576, left-hand column, first paragraph of document D3). At the end of document D3, it is stated: "*(t)he functions of WSX-1/TCCR in the context of the cytokine network will no doubt be clarified by identification of the ligand and coreceptors, if any, for this molecule*" (cf. page 576, right-hand column, paragraph before the heading "Experimental Procedures" of document D3). Document D2 also concludes that "*(t)he apparent specificity of the phenotype described here makes TCCR and its potential ligand candidate targets for therapeutic intervention in Th-1 mediated autoimmune disease and allograft rejection*" (cf. page 919, right-hand column, last paragraph), which, as shown in point 15 above, are two conditions explicitly mentioned in the present application.

18. It is only in document D5, published in 2002 (six years after the priority date of the present application), that the cytokine IL-27 is identified as the natural ligand of the Zcytor1/WSX-1/TCCR receptor. This cytokine is shown to be heterodimeric and to mediate the biological effects of the cytokine Zcytor1/WSX-1/TCCR (IL27R) receptor. Later literature (2004 and 2005) also on file demonstrate the role of IL-27 in several diseases associated with inflammatory and destructive processes arising from uncontrolled or inadequately up-regulated cellular immune response (cf. document D7).

The reasons for the refusal given in the decision under appeal

19. Although recognising that the predicted role of the protein Zcytor1 in proliferation, differentiation and/or activation of immune cells was "reasonably credible", the examining division denied the industrial applicability of the claimed invention on the basis of, essentially, the following two reasons: **i)** the use of a computer-assisted alignment as disclosed in the application did not allow any concrete conclusions to be made as to the actual specific function of the protein, because such studies provided only speculation of a vague nature and no specific therapeutic or diagnostic use could be ascertained therefrom; **ii)** the Zcytor1 receptor was only a research tool whose importance lay in establishing a research programme and whose disclosure was only the first step in the quest for industrially applicable matter.

Is the claimed subject-matter industrially applicable?

20. As seen above with reference to the case law of the boards of appeal, the disclosure of the function of a newly discovered protein is of utmost importance when examining the issue of "industrial applicability" as the function is the gateway to understanding the concrete benefits which may derive from exploiting the invention industrially. As shown by T 870/04 (*supra*), the mere characterisation of the structure of a protein may not be enough to comply with Article 57 EPC if no profitable use of the protein is disclosed. On the other hand, T 338/00 and T 604/04 (*supra*) show that a positive answer can be given in spite of the absence of actual experimental data, if a profitable use can

readily be identified on the basis of the description taking into account common general knowledge. This demonstrates that this matter can only be decided in each case on its own merits according to the particular technical circumstances (extent of disclosure, background art, post-published evidence etc.)

21. In the present case, based on computer-assisted sequence homology studies and on tissue distribution studies, the Zcytor1 receptor was identified in the application as a putative member of the hematopoietin receptor family and it was assigned a role in proliferation, differentiation and/or activation of immune cells and thus a possible role for its ligands in therapeutic conditions associated with the functioning of the immune system. Admittedly, no experimental evidence for the suggested role of the receptor and/or its ligands is made available in the application. Later evidence, however, confirmed this sort of "educated guess", which the examining division considered to be - in its own words - "reasonably credible".

22. The fact that the putative function of the Zcytor1 receptor was assigned in the examples based on computer-assisted methods, rather than on the basis of traditional wet-lab techniques, does not mean that it has to be automatically disregarded or excluded from a careful and critical examination. There is no "all-encompassing" approach, and certainly not a "throw-into-the-bin" approach, for these in-silico examples. Their probative value has to be examined on a case-by-case basis regarding the nature of the invention and the prior art relating thereto. Such

- methods of analysis are increasingly becoming an integral part of scientific investigations and can often allow plausible conclusions to be made regarding the function of a product before it is actually tested.
23. The present application refers to conventional computer-assisted methods for alignment of sequences and calculation of percent sequence identity. Both the referred methods and the parameters indicated in the application (gap opening penalty, gap extension penalty, scoring matrix, etc.) are well-known and standard in the field (cf. page 10, line 23 to page 12, line 2 of the published application and page 917, left-hand column, lines 13 to 15 of document D2). No objections have been raised by the examining division, nor does the board see any, in this respect.
24. As regards the results derived from the computer-assisted method, it is noted that the application indeed does not disclose any sequence alignment nor does it provide the actual percentage of sequence identity with other known members of the hematopoietin receptor family. However, based on the general structure of the Zcytor1 receptor and the presence of several specific structural features, the Zcytor1 receptor is clearly identified as a putative member of this hematopoietin receptor family (cf. point 13 *supra*). There is no evidence on file showing that this conclusion is flawed or that it is based on wrong assumptions. Nor does the board on the basis of the facts and evidence on file see any reason to conclude otherwise. Under these circumstances, the post-published evidence, which confirms the preliminary

finding and actually supports the conclusion, cannot be ignored.

25. It is based on this computer-assisted identification and on the results of the tissue distribution of Zcytor1 expression that the application suggests a possible role for the Zcytor1 receptor, namely "*in proliferation, differentiation and/or activation of immune cells*" and more specifically a role "*in early thymocyte development and immune response regulation*" (cf. point 14 *supra*). Although no disclosure is made of any actual ligand of the said receptor, the application describes fused and non-fused forms of soluble antagonist ligands. The relevant question is thus whether these indications suffice to support a profitable use of the invention in industry in the sense outlined above, and, if so, the acknowledgement of industrial applicability.
26. Although considering the suggested role to be "*reasonably credible and [...] confirmed*", the examining division considered it to be "*so vaguely defined that no specific biological function which would implicate a therapeutic use or a diagnostic use has been defined*". In this respect, the examining division also observed that "*the members of the family all obviously have different functions*" (cf. Section VII *supra*).
27. It might well be possible that members of a structurally related family have, notwithstanding their related structure, a different activity and function. However, there is no reference to the prior art in the decision under appeal which supports such a case in the

hematopoietin receptor family. In fact, from the prior art cited in the application and concerned with this family of receptors (cf. page 7, lines 18 to 19, page 9, lines 23 to 25), it may be derived that, although none of these members are precisely interchangeable in terms of their biological action, there is considerable redundancy of action as well as an ability to elicit, under certain conditions, similar biological responses. Even more important is the fact that this prior art does not cast significant or serious doubts on the suggested role of the Zcytor1 receptor. Thus, the assumption (or "educated guess") made in the patent application is plausible.

28. The question remains whether this role is so "vaguely defined" that no practical application or profitable use in the sense of Article 57 EPC can be envisaged.

29. Whereas the structural characterization of a protein might be directly derived from the genome, its function cannot normally be derived in a straightforward manner therefrom. The function of a protein (and thus of the nucleic acid encoding it) can be seen at different levels. These include: **i)** the biochemical activity of the protein (protease, endonuclease, ion channel or pump, etc.), i.e. its molecular function; **ii)** the function of the protein in cellular processes (apoptosis, secretion pathway, etc.), i.e. its cellular function; and **iii)** the influence of those cellular processes within a multicellular organism, i.e. in a general and more complex network within a multicellular organism (cancer, inflammation, immune responses, etc.), this being its biological function in a broad sense. Each of these levels, particularly the cellular and

- biological function, may not be restricted to a very single (objective) function but may encompass multiple functions arising from all the different possible protein complexes (units of macromolecular organization) in which the protein might participate or contribute. In fact, the latter is more the rule than the exception.
30. The elucidation of one of these particular levels of function might result, under certain conditions, in a straightforward industrial application, even though the other levels of activity remain completely unknown or only partially characterized. There might also be cases where the protein derives its industrial applicability just at the level of its specific structural features such as, for instance, an amino acid composition that could render it advantageous for animal feeding, (standard) calibration purposes, etc and completely independent of its biochemical, cellular and/or biological function. For the purpose of Article 57 EPC and Rules 23e(3) and 27(1)(f) EPC, none of these levels is more fundamental, i.e. "more specific" or "less vague" in the words of the decision under appeal, than the other ones insofar as at least from one of these levels a practical application (a profitable use in a wider sense, cf. points 5 and 6 *supra*) is derivable in a straightforward manner.
31. In the present case, the suggested role of the Zcytor1 receptor corresponds to the level of the biological function and the practical applications or the concrete technical benefits derived therefrom are clearly disclosed in the present application, namely the stimulation of cell-mediated immunity and of lymphocyte proliferation by agonist ligands of Zcytor1 and the

suppression of the immune system by antagonists of the Zcytor1 receptor (cf. page 20, lines 5 to 18). Although the details of the biochemical activity and the cellular function of the Zcytor1 receptor have not been elucidated in the application, the (therapeutic) treatments directly derivable from the biological function identified by the computer-assisted method cannot be considered to be so "vaguely defined" that they do not suggest any therapeutic or diagnostic use. On the contrary, the treatments referred to in the application are specifically in relation to the function plausibly attributed to the molecule, and are in the areas of rheumatoid arthritis, multiple sclerosis, diabetes mellitus, etc. In this respect, this case differs from that of decision T 870/04 (*supra*) where no clear role for the claimed molecule was identified (cf. point 10 *supra*). The Zcytor1 receptor, and more particularly the products related thereto, such as the extracellular Zcytor1 fragment, cannot be seen as a mere tool for research undertaken for its own sake or in the quest to provide industrially applicable matter, but rather as a product with a plausible application in an industrial (medico-pharmaceutical) activity. Thus, on this issue, the board cannot concur with the conclusion arrived at by the first instance.

32. In the light of the above considerations, it is concluded that the claimed subject-matter as a whole is industrially applicable and thus fulfils the requirements of Article 57 EPC and Rule 23e(3) EPC.

Referral to the Enlarged Board of Appeal

33. The appellant has suggested a number of questions in relation to Article 57 and Rule 23e(3) EPC to be referred to the Enlarged Board of Appeal in case this board should not agree with its position that the claimed subject-matter complied with those provisions of the law. As that is not the case, there is no reason for a referral of any questions to the Enlarged Board of Appeal.

Remittal to the first instance for further prosecution

34. The decision under appeal was based only on an objection under Article 57 EPC and Rule 23e(3) EPC. There is no mention of the other requirements of the EPC, in particular of those of Articles 56 and 83 EPC, which are distinct from those of Article 57 EPC. Although the technical solution disclosed in the application has now been found to be "susceptible of industrial applicability" (Article 57 EPC), it still has to be assessed whether this solution is non-obvious in the light of the prior art (Article 56 EPC) and whether it has been sufficiently disclosed for a skilled person to carry it out without undue burden (Article 83 EPC). Therefore, the board considers that it is appropriate to exercise its discretion under Article 111 EPC and to remit the case for further prosecution to the first instance so as to examine these outstanding substantive issues.

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 for further prosecution on the basis of the main request as filed with the statement of grounds of appeal.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani