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**SUBJECT:** EPO case law on in silico (computer based) analysis of genes and proteins

**PURPOSE:** For information

**TABLED TO:** All Attendees



**EPO Board of appeal decisions on genomics relating to in silico (computer based) analysis and industrial applicability of genes and proteins**

**Summary**

Examiners at the European Patent Office (EPO) have announced their opinion that applications relating to genomics based on in silico analysis without wet experiments should not be allowed (Siobhán Yeats, Global Patent Management, October 2001 p.30-32).

Now there are some technical board decisions at hand, wherein the industrial applicability of proteins has been decided or suggested by in silico analysis or structural comparison with other known proteins. In cases T 870/04, T 1329/04 and T 0609/02 industrial applicability was denied whereas in T 338/00, T 604/04 and T 0898/05 industrial applicability was recognised.

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. The probative value has to be examined on a case-by-case basis regarding the nature of the invention and the prior art relating thereto (catchwords of T 08998/05)

However, for the purposes of industrial applicability according to Article 57 EPC, the skilled person must be able to recognise that the invention has an immediate and concrete benefit. This must be derivable directly from the description, if it is not already obvious from the nature of the invention or from the background art (catchwords of T 08998/05).

To have a patent granted on in silico analysis of genes and proteins, the effect of the genes or the proteins should be substantial and credible on the effective date i.e. priority or filing date (T 0609 p.13). Decisions are made on a case by case basis. Criteria involved for the decision are: inventive step A 56 EPC i.e. providing a non-obvious solution to a technical problem; industrial applicability A 57 EPC i.e. indicating how to exploit the invention, sufficiency of disclosure A 83 EPC and clarity and support A 84 EPC.

The John Hopkins case T 1329/04 for example relates to a new protein with 34% homology with the TGF beta family. The EPO found that it was not likely at the priority date that the protein really belonged to this family due to the low homology percentage. No wet experiments were disclosed at the filing date. Only three years after the priority date could the applicants prove that the protein in fact belonged to the TGF beta family. However, this was deemed too late and a patent was not allowed.

In case T 604/04 it was disclosed that the polypeptides themselves were respectively 34% and 36% identical to the known IL-8 receptor. The polypeptides were identified as members of the G-protein-coupled super family of receptors, which bind members of the PF4A family of chemokines and, insofar, indicated what their function could be. It was observed that they bear greater similarity to the IL-8 receptor than other receptors.



Yet, there was no characterisation of their ligands, and thus the 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. Thus, it was credible on the filing date what their role might be. Inventive step was recognised because the cloning of the genes was not straightforward.

### **Industrial applicability not recognised**

T 870/04.

The Examining Division rejected the application. The applicant appealed and the Technical Board of Appeal rejected the application.

The invention related to a new isolated human polypeptide designated BDP1 ("Brain Derived Phosphatase1") and was shown to belong to the PTPase (protein tyrosine phosphatases) PEST family characterised by the occurrence of the PEST sequences. BDP1 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 concluded that, although the application described a polypeptide, means and methods for making it and its prospective use for basic scientific activities, it identified no practical way of exploiting it in at least one field of industrial activity.

The BDP1 was identified as a PTP-PEST but there was no clear identification of its function or use, and the prior art did not attribute clear functions to PTP-PESTs as a class.

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 themselves.

T 1329/04

The Examining Division rejected the application. The applicant appealed and the Technical Board of Appeal rejected the application.

The application related to a new GDF-9 protein which had 34% homology with the TGF- $\beta$  family. Other members of the family had 70 to 90% homology and comprised a most striking structural feature namely seven cysteine residues. The GDF-9 comprised only six. GDF-9 could not be clearly and unambiguously identified as a member of the TGF- $\beta$  superfamily by only using a "structural approach" according to the board.

There was no evidence at all to prove that GDF-9 played a role similar to that of the transforming factor- $\beta$  (as was the case for all of the factors, which initially served to define



the superfamily). The application only disclosed that expression of GDF-9 is localised in ovarian tissues.

The appellant filed post-published evidence establishing that GDF-9 was indeed a growth differentiation factor. This was not regarded as supportive of evidence, which should have been given in the application as filed since there was not any. The said post-published documents were the first disclosures going beyond speculation.

Even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve. Therefore the appeal was dismissed. This case is different from case T 0604/04 (see below) in that the structure did not conform with the family and no function was disclosed.

#### T 0609/02

The patent was maintained after opposition. However, the applicant appealed to have a further claim 6 granted. It related to the use of a steroid hormone or analogue thereof which fails to promote transcriptional activation of glucocorticoid receptor- or retinoic acid receptor-responsive genes, for the preparation of a pharmaceutical for the treatment of AP-1 stimulated tumour formation, arthritis, asthma, allergies and rashes, said hormone being identified by the method according to the previous claims.

The patent specification provided no evidence at all relating to the invention in claim 6. No steroid hormone was identified as binding to the hormone receptor in such a way that the so-formed complex will disrupt AP-1 stimulated transcription and at the same time fail to promote steroid hormone regulated transcription. No data of any kind were presented indicating that such a hormone (if it were identified) could have an impact on any of the listed specific diseases.

The appellant provided post-published evidence showing that steroid hormones such as needed to carry out the use according to claim 6 were later structurally identified and that they, indeed, have an effect on AP-1 stimulated transcription

According to the board sufficiency of disclosure must be satisfied at the effective date of the patent, i.e. on the basis of the information in the patent application together with the common general knowledge then available to the skilled person. Acknowledging sufficiency of disclosure on the basis of relevant technical information produced only after this date would lead to granting a patent for a technical teaching which was achieved, and, thus, for an invention which was made, at a date later than the effective date of the patent. The general principle that the extent of monopoly conferred by a patent should correspond to, and be justified by, the technical contribution to the art, has to be kept in mind.

The board found that claim 6 covered limitless and untried downstream developments in relation to yet to be demonstrated molecular mechanisms. It amounts to no more than an invitation to set up further research programs for which no guidance is forthcoming.

There must be a clear and accepted established relationship between the shown physiological activities and the disease. Once this evidence is available from the patent application, then post-published (so-called) expert evidence (if any) may be taken into account, but only to back-up the findings in the patent application in relation to the use of the ingredient as a pharmaceutical, and not to establish sufficiency of disclosure on their own.



## **Industrial applicability recognised**

### T 338/00

The examining division refused the application for lack of inventive step, applicant appealed and the case was granted. Industrial applicability was however commented on by the technical board of appeal.

The application claimed a heterodimeric receptor or dimer and a method to modulate transcription activation of a gene. The receptors belonged to the steroid/thyroid super family of receptors having highly conserved amino acids in the DNA binding domain

The application provided evidence on the use of these heterodimers for modulating suitable transcription expression systems. There were references to the possible relevance of the disclosed heterodimers in several physiological processes (development, differentiation and homeostasis) in the application. Moreover, the application comprised an in vitro method for screening the suitability of other members of the steroid/thyroid hormone receptor super family to form heterodimers with RXR and, implicitly, its possible use to screen further compounds for their ability to modulate and/or to alter the disclosed co-operative interactions. Thus the application was found to fulfil the industrial applicability requirement of Article 57.

It was found that heterodimeric receptors comprising one member selected from isoforms of RXR and COUP-TF presented inventive step and the application was granted.

### T 604/04

The application was granted, opposed and granted again but claims relating to polypeptides of two of the figures were not allowed because the cloning was obvious and no credible function and no technical useful properties were presented.

The application related to polypeptide receptors the structural characterisation of 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.

It was disclosed that the polypeptides themselves are respectively 34% and 36% identical to the IL-8 receptor. The polypeptides were identified as members of the G-protein-coupled super family of receptors and it was observed that they bear greater similarity to the IL-8 receptor than other receptors.

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. This was contrary to the situation in T 1329/04 and T 870/04.



The board found that the cloning was not obvious because it was performed in a manner different from the prior art, which brought about that the new receptors were found. Applying the prior art technology would not have revealed the receptors.

The application was granted again now also with a claim 18 directed to "An isolated platelet factor 4 superfamily receptor (PF4AR) polypeptide having at least an 85% amino acid sequence homology with the translated amino acid sequence of figure 4 or figure 5."

However, antibodies against the receptors were not allowed because no diseased state caused by the "misfunctioning" of the receptors were identified.

#### T 0898/05

The application was refused by the examining division and appealed. The board of appeal recognised industrial applicability and referred it to the examining division who granted it directly.

The application disclosed the nucleotide sequence and the encoded amino acid sequence of the human transmembrane receptor Zcytor1 and the sequences of a natural splicing or allelic variant thereof. Based on the general structure of this receptor and several specific structural features, the Zcytor1 receptor was identified by computer-assistance as a putative member of the hematopoietin receptor family. 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\*).

Based on this computer-assisted identification and on the results of the tissue distribution of Zcytor1 expression the application suggested 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*". Although no disclosure was made of any actual ligand of the said receptor, the application described fused and non-fused forms of soluble antagonist ligands.

The application further disclosed studies on the tissue distribution of the Zcytor1 expression. The analysis of these studies showed that the expression of the Zcytor1 receptor is "*widespread*". 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.

Several post-published documents D2 and D3 - published respectively four and five years after the priority date of the present application - 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- $\gamma$  and induction of Th1 responses but not for its maintenance

In document D5, published in 2002 (six years after the priority date of the application), 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) demonstrates the role of IL-27 in several diseases associated with inflammatory and destructive processes arising from uncontrolled or inadequately up-regulated cellular immune response.



The application did not disclose any sequence alignment nor did 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 was clearly identified as a putative member of this hematopoietin receptor family according to the board. There was no evidence on file showing that this conclusion is flawed or that it is based on wrong assumptions. Nor did 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 according to the board.

Catchwords of T 08998/05

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.

However, for the purposes of industrial applicability according to Article 57 EPC, the skilled person must be able to recognise that the invention has an immediate and concrete benefit. This must be 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. Sufficiency of disclosure must be shown to exist at the effective date of a patent.

Helène Fagerlin 08 03 2008