Recent practice in biotechnology patenting at the EPO

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Summary

Patent practice at the European Patent Office for biotechnological inventions is presented. The patentability of different inventions in DNA field are discussed.

Key words:
Biotechnology, patents, EPO.

1. Introduction

Biotechnology patent practice at the EPO is at present dominated by three main issues:

– The first is the European Union Directive 98/44/EC on the legal protection of biotechnology inventions, which was inserted into the European Patent Convention (EPC) as new Rule 23b through 23e (entered into force on 01.09.1999).

– Another very important matter is the decision G1/98 (OJ 3/2000, 111) of the Enlarged Board of Appeal relating to whether plants are patentable under the EPC in the light of Article 53(b) EPC, which excepts patentability, inter alia, plant or animal varieties.

– Finally, there is much debate about whether inventions in the field of genomics, such as expressed sequence tags (ESTs), which involve no more than automated sequencing, or such as DNA sequences which encode putative proteins for which no function has been demonstrated, are patentable or not.

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This article is focussed on the latter issue and the prevailing view of the EPO regarding whether such inventions meet the requirements for patentability. The last few years have seen a renewed interest in filing patent applications for ESTs or DNA sequences determined by automated sequencing, which encode putative proteins (or fragments of proteins) for which no function or activity has been demonstrated or confirmed. The EPO does not yet have any case-law on such applications, since only a few applications have reached the stage of being decided upon (granted or refused) in examination, let alone have the Boards of Appeal, the final instance in the EPO, ruled upon such a case.

Table 1

Articles and Rules of the EPC (and PCT) relevant for Examination

Patentability	Article 52 EPC	
Novelty	Article 54 EPC	(Art. 33(2) PCT)
Inventive step	Article 56 EPC	(Art. 33(3) PCT)
Industrial application	Article 57 EPC, Rule 27(1)(f), Rule 23e(3) EPC	(Art. 33(4) PCT R. 5(vi) PCT)
Disclosure	Article 83 EPC, Rule 27(1)(e), (f) EPC	(Art. 5 PCT)
Clarity/Support	Article 84 EPC	(Art. 6 PCT)
Unity	Article 82 EPC	(Art. 34(3) PCT)

2. Problems encountered with applications for DNA sequences encoding putative proteins without confirmed function

The following example of a claim illustrates problems encountered with this type of applications from the field of genomics:

1. An isolated nucleic acid molecule comprising a polynucleotide sequence selected from the group consisting of:

a) a polynucleotide having at least 53,9% identity to a polynucleotide encoding a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:1;

b) polynucleotide which is complementary to the polynucleotide of a);

c) a polynucleotide comprising at least 15 sequential bases of the polynucleotide of a) or b).

The application discloses a cDNA sequence (cDNA is a copy of the mRNA transcribed from genomic DNA) of an organism and a hypothetical protein encoded by said sequence. The nucleotide sequence encoding said hypothetical protein has about 53.9% identity with other nucleotide sequences encoding proteins from other organisms having more or less speculative functions. As stated in the description

this identity may be over the whole length, however fragments are included. The description often starts from an EST sequence for which a computer-assisted homology search against public databases was carried out. Next, the complete putative coding sequence was assembled from a cDNA library using PCR techniques. The description then speculates that the protein which may be encoded by said sequence is structurally related to other proteins using computer-assisted sequence alignments. For example, the protein has a motif, a domain, an "X"-box in common with other prior art proteins being members of family "Y". These prior art proteins although belonging to this family "Y" have different specific functions. For instance, in case of a receptor the effects of the family ligands and the receptors of this family are varied in a signal transduction pathway and the members of family "Y" may influence numerous functions, thus there is a large number of biological effects to be attributed to different members of this family.

The description lists all the known or possible functions/activities for the known members of family "Y", e.g. participation in signal transduction pathway, ion flow etc. Furthermore, the description lists possible diseases in which the polypeptide could play a role.

The description lists possible uses ("utilities") for the nucleotide sequence/polypeptide/antibody raised against said polypeptide. These uses comprise:

- target for new drugs;
- query sequence to search in public databases;
- starting point to establish the biological activity or function of the polypeptide;
- search for ligands, agonists, antagonist.

It has not been demonstrated in the application that the hypothetical protein of this application has any of the speculative functional properties of the prior art proteins (family "Y") to which it is homologous. It may not even have been demonstrated that the cDNA sequence is translated into polypeptides meaning that it doesn't have any function at all.

3. Are applications based entirely on sequence data complete inventions worthy of a patent?

The question to be asked is: is there an invention or is this sequence a discovery?

Discoveries are not patentable under the European Patent Convention (Art. 52 (2)(a) EPC. Rule 23e(1) stipulates that the human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.

Also the Guidelines for Examination state that: To find a substance freely occurring in nature is also a mere discovery and therefore unpatentable. However, if a substance found in nature has first to be isolated from its surroundings and a process for obtaining it is developed, that process is patentable. Moreover, if the sub-

stance can be properly characterized, either by structure, by the process by which it is obtained or by other parameters and it is new in the absolute sense of having no previously recognized existence, then the substance per se may be patentable.

Interestingly, Craig Venter's view given in a CNN interview is the following: "We consider that we are making discoveries, we're not making inventions with the primary sequencing".

The term "isolated" in the example of the claim distinguishes the nucleic acid molecule from the sequence found in nature, in that a copy of the genetic information occurring in nature was made and this copy was than presented isolated from the genetic information in the chromosome. The nucleotide sequence of previously cited claim 1 therefore represents a copy of an isolated genetic information.

In view of the use stated in the description "Starting point to establish the biological activity or function of the polypeptide" the description admits that the function or biological activity of the putative protein has not yet been determined or confirmed. Thus it is not properly characterized.

All that such an application provides is a starting point or an invitation to carry out a research programme for the next years. This cannot be called a **complete** invention.

4. Is the requirement of industrial application fulfilled?

Article 57 EPC, which relates to industrial application, reads:

"An invention shall be considered as susceptible of industrial application if it can be **made or used** in any kind of industry, including agriculture". This Article has to be read together with Rule 27(1)(f) EPC that "The description shall 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". With regard to nucleotide or polypeptide sequences it must be emphasized that Art. 57 EPC cannot be interpreted as meaning that merly "making" the sequence or the polypeptide fulfils the requirements of this Article.

There is no doubt that the sequences or polypeptides can be made. However, is this sufficient to render the claimed invention industrially applicable? Making nucleic acid molecules or polypeptides without any purpose is technically and industrially not meaningful.

Thus the use requirement of Art. 57 EPC must be fulfilled for chemical compounds such as nucleic acid molecules and polypeptides. This means in general that there must be a function/biological activity attributed to said specific nucleic acid molecule or polypeptide that shows its industrial applicability or at least makes it plausible.

For further clarification Article 57 EPC has also to be read together with Rule 23e(3) EPC that "The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application".

Moreover, according to Rule 23b(1) EPC,"Directive 98/44/EC on the legal protection of biotechnological inventions shall be used as a supplemental means of interpretation."

Recitals (22), (23) and (24) of this Directive (98/44/EC) clearly state that a mere sequence without indication of a function is not a patentable invention. Hence the existence of Rule 23e(3) EPC is an indication that Art. 57 EPC cannot be interpreted to mean that making the sequence or the polypeptide fulfils the requirement of Article 57 EPC. The existence of Rule 23e(3) in view of the Directive unambiguously requests the examination of the question whether the "use" requirement of Art. 57 EPC is fulfilled.

Regardless of Rule 23e(3) EPC, it even follows from Art. 57 and Rule 27(1)(f) EPC alone that if the invention is the usefulness of a product, which clearly is the case for chemical products, such as polynucleotides or polypeptides, the application should in these cases teach how the product should be used in industry in a technically meaningful way.

If the only use for the sequence or the polypeptide it encodes is for use as a target for new drugs, a probe, a query sequence to search in databases or to assess the physiological function of the polypeptide, it would be nothing more than an enumeration of possible functions or activities; an invention yet to be made. Such an enumeration and the listing of, e.g. diseases the nucleic acid molecule or putative protein is involved in, is not sufficient and of no aid for the skilled person. If the skilled person has the burden to find out which of these functions or diseases is the relevant one if any, the requirements of Art. 57 and Rule 27(1)(f) EPC cannot be considered to have been met. Moreover, such uses are research uses; they cannot be regarded as equivalent to industrial uses. For example, if the drug has not yet been developed, its potential use in any kind of disease state, and thus in any kind of industry, has still to be determined. Thus it must be concluded that the requirement of Article 57 EPC is not fulfilled.

5. Inventive step

The third questions is: is the product, the nucleotide sequence, inventive?

The EPO at present generally denies an inventive step for applications based on pure sequencing if nothing is determined about the function or activity of the polypeptides encoded by the claimed polynucleotides.

What problem is solved by the polynucleotide sequence?

Providing means for the diagnosis of a disease (e.g. of infection by a bacterial pathogen)?

Probe?

Target for new drugs?

Query sequence?

The sequences alone without special functional features are not apt to distinguish them from the bulk of other sequences present in a cell. It has not been demonstrated, or at least been made plausible, that these sequences or the polypeptides they encode are suitable for the purposes of diagnosis for the listed diseases or targets for new drugs, that is, that they are relevant for the diseases or are essential for the pathogen and thus suitable as a target for drugs to be developed.

Thus it must also be shown that the alleged solution indeed solves the problem (T248/85, OJ 1986, 261; T 939/92).

Furthermore, in case of a receptor without a determined function, in which disease is this polypeptide (receptor) involved?

Which function or biological activity should be altered or modulated in order to overcome such a hypothetical disease?

In the absence of a confirmed function for the polypeptide encoded by the claimed sequences, the problem to be solved by such an application is simply reduced to the problem of the provision of new sequences encoding proteins. If no technical effect (function or biological/physiological activity) was determined in the application, the solution, that is the sequence, has to be seen merely as "enriching chemistry" (T939/92). In the decision of the Board of Appeal (T939/92) the problem was to be seen as "provision of further (or alternative) chemical compounds". This problem, however, was rejected in the decision of the Board of Appeal as "minimalist" and not technically meaningful. Said "enriching chemistry" was considered to lack an inventive step.

With regard to the example of a sequence (polynucleotide) it must thus be concluded that in the absence of any confirmed (proven or probable) function or use the **problem** is the provision of further polynucleotides encoding (putative) polypeptides for the hypothetical use as probes, targets, etc. The **solution** is a nucleotide sequence encoding a polypeptide/protein chosen from a host of possible sequences, this solution is a **non-inventive selection**.

Additionally, it should be noted that the technical effect must be achievable over the whole range of applications claimed; that is for all the claimed polynucleotides encoding polypeptides which have 53.9% identity to a polynucleotide encoding a polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 1.

Moreover, there are examples from the art known to the skilled person that even minor changes in the amino acid sequence of a protein may result in changes of the biological activity of the protein. An example for this is the Wilms tumor suppressor WT1. The presence or absence of three consecutive amino acids due to alternative splicing changes the biological function of the splice isoforms from association with splice factors to association with the transcriptional apparatus

(M. Ladomery et al, EMBL, SALK, EMBO Conference on Oncogenes & Growth Control 2000 Heidelberg, May 13-17, 2000 page 18).

Essentially, a mere structural relationship in terms of % sequence identity and further without limitation to the entire length of the given sequence, thus including all kinds of fragments, and without limitation to a determined/confirmed function, is not inventive (and maybe not even novel).

6. Concluding remarks

Finally, other possible objections are lack of unity of invention, in cases where a number of unrelated polynucleotide sequences are claimed, sufficiency of disclosure, and lack of support of claims to medicaments involving polypeptides encoded by the sequences and other types of claims based on an activity yet to be determined.

However, in other cases, claims for sequences without determined biological function may be patentable, if e.g. these sequences relate to repetitive sequences in the genomic DNA (the chromosome) which repetitive sequences differ by number in individuals and if these sequences can be used, for example, in the determination of sibships.

In conclusion, however, in the last instance the issue of patentability of ESTs and nucleotide sequences encoding putative polypeptides/proteins having a speculative function only based on structural homology to some parts of a known protein will only be resolved when a case or cases is/are decided by the Boards of Appeal.

Footnote:
This article represents the personal opinion of the author.