



THE ROLE OF THE FUNCTION OF DNA SEQUENCE BEFORE AND AFTER GRANT



Recent European decisions have provided much to think about for practitioners concerned with DNA sequences. Caroline Pallard and Bart Swinkels investigate.

Before grant

Industrial application is one of the requirements of a European patent (EP). Subsequently, the EC Biotech Directive 98/44 provided more explanation of the concept of industrial application of DNA sequences: the industrial application of a DNA sequence must be disclosed in the application. A DNA sequence without indication of a function is not a patentable invention. If a protein is to be produced, its function should be defined in the application.

Several EP case law decisions issued on industrial application of DNA sequences-related inventions shed new light on the concept of ‘function’ when applied to a protein/corresponding DNA sequence.

T0870/04

The European Patent Office Board of Appeal held that the requirement of industrial application was not met. It held that the only practicable use suggested is to use the BDP1 phosphatase to find out more about its natural function. This kind of activity could not be considered as industrial application, but rather research.

Therefore, even if the structure and function of a protein is disclosed, the requirement of industrial application is not necessarily met if:

- The function is complex and not fully understood
- No disease has been identified that is linked to an excess or deficiency of the protein and
- No other uses have been disclosed.

T898/05

The board held that the requirement of industrial application was met. It provided a new definition of function when applied to a protein: “The function of a protein can be seen at different levels. These include:

- The biochemical activity of the protein or molecular function (protease, etc.)
- The function of the protein in cellular processes or cellular function (apoptosis, etc.)
- The influence of those cellular processes within a multicellular organism or biological function (cancer, immune response, etc.)”

It is concluded that the elucidation of one of these functions may result in an invention fulfilling the requirements of industrial application even if other functions are not yet elucidated. In this specific case, the molecule and cellular functions were not disclosed. However, the biological function of the protein disclosed in the application (immune response) provides an “immediate concrete benefit” derivable from the application.

Therefore, even if the structure of a protein is disclosed without a molecular function, the requirement of industrial application may be met.

EP decision	Amino acid Nucleic acid sequences	Presence of conserved domains	Function -molecular (M) -cellular (C) -biological (B)	Disclosed use	Tissue distribution	Data in the application supporting therapeutic role	Post-published data on therapeutical use	Industrial application
T870/04 BDP1 Brain Derived Phosphatase 1	Yes	No	M (Tyrosine phosphatase)	“Possible anti cancer”	No	No	No	No
T898/05 Zcytor1 Cytokine Receptor	Yes	Yes	B (immune response)	Immune response	Yes	No	Yes Confirm as IL27receptor	Yes
T18/09 TNF ligand	Yes	Yes	B (immune response)	Long list of diseases	Yes	No	Yes	Yes

T0018/09

On appeal, the question of industrial application raised whether the information contained in the patent in itself “suffices to suggest a practical way to exploit the claimed invention which is centred on Neurokine- α , thereby providing an ‘immediate concrete benefit’ as defined in T898/05”.

As in T898/05, the board concluded that in light of the common knowledge of the TNF ligand superfamily, no serious doubts could be cast on the assumption made in the patent concerning the role in T cell proliferation. In addition, this suspected role is plausible and had been supported by submitted post-published evidence.

The board further explained that the fact that an impressive list of potential uses was disclosed in the application was not detrimental to the validity of the patent, provided the patent in itself delivers sufficient technical information to satisfy the requirement of industrial application.

Therefore, if the structure of a protein is disclosed and a therapeutic role is assumed based on it belonging to a well-known class of receptor and on tissue expression data, the requirement of industrial application may be met.

However, the UK patent derived from this EP patent had been invalidated for lack of industrial application by the UK Court of Appeal. That court held that the biological activities of TNF ligand were still poorly understood and it could not recognise why an assumption of an effect on T cell activity would represent a valid basis for industrial application.

This case is pending before the UK Supreme Court. The hearing is scheduled for July 2011.

When drafting an EP patent application protecting a DNA sequence, at least “one level of function” of the corresponding protein must be disclosed in the application. This must lead to an immediate concrete benefit derivable from the application as filed. The presence of tissue distribution data may provide a first line of evidence of industrial application. In addition, in view of the corresponding UK case of T18/09, it is advisable to incorporate experimental data at least in a cellular model further substantiating a therapeutic role. The submission of post-published data to support the preliminary data present in the application is advisable.

After grant

Having overcome the hurdles of industrial application and being the proud owner of a European patent with product claims directed at DNA sequences, you may well be facing a new

challenge in enforcing your patent in view of the recent decision in *Monsanto v CEFETRA* by the European Court of Justice (ECJ).

In various European countries, including the Netherlands, Monsanto sought to enforce its European patent EP0546090 with product claims on DNA molecules encoding an enzyme providing resistance against the Roundup™ herbicide in order to stop import of soy meal from Argentina. The soy grown in Argentina did indeed contain the claimed gene to provide herbicide resistance. After harvesting the soy beans, their oil is extracted, and the remains are crushed, dried, heated and pressed into soy meal pellets, before being shipped to Europe. After these harsh treatments, the soy DNA present in the soy meal pellets consists mostly of fragmented DNA. Yet, trace amounts of intact DNA molecules comprising the herbicide resistance gene can still be detected in the processed soy meal.

Monsanto argued that the trace amounts of intact DNA molecules residually present in soy meal imported into Europe infringed its patent under national patent laws in Europe, because as Monsanto alleged, it should enjoy absolute product protection. The soy meal importers, on the other hand, argued—*inter alia* on the basis of Article 9 of the EC Biotech Directive 98/44—that the protection of Monsanto’s patent should not extend to products wherein the claimed DNA molecules, if present at all, are residually present and incapable of performing any function.

The District Court of The Hague decided to refer several questions to the ECJ, including: should Article 9 of the directive provide protection when the DNA sequence is part of a material (meal) and is not performing its function at the moment of infringement, but did perform the same or could possibly (after isolation) again perform its function, and does Article 9 prevent the national patent conferring absolute protection on the DNA, regardless of whether the DNA performs its function?

Article 9 of the directive provides that:

“The protection conferred by a patent on a product containing or consisting of genetic information shall extend to all material, save as provided in Article 5(1), in which the product is incorporated and in which the genetic information is contained and performs its function.”

The Court of Justice answered the questions as follows:

1. Article 9 does not confer patent protection when the patented product is contained in soy meal, where it does not perform the

function for which it is patented (irrespective of whether it did perform that function previously or would possibly again be able to perform that function after its extraction and reinsertion into a living cell).

2. Article 9 effects an exhaustive harmonisation of the protection it confers, with the result that it precludes the national patent legislation from offering absolute protection to the patented product as such.
3. This ruling is applicable to all patents in the EU irrespective of their filing or issuance date.
4. This interpretation is deemed compatible with Articles 27 and 30 of the TRIPS Agreement.

We believe that even though Monsanto may have been overextending its European patent rights to compensate for a lack of patents in Argentina, this decision of the ECJ is not in line with the intention and purpose of the Biotech Directive when it was drafted and adopted by its legislators. The ECJ has referred to Recitals 23 and 24 in the preamble of the directive for justification of the purpose-bound protection of DNA sequences it now introduces. However, Recitals 23 and 24 are not concerned with protection conferred by claims on DNA sequences. Rather, Recitals 23 and 24 address one of the requirements of patentability *per se* of DNA sequences, i.e. their industrial applicability. They were prompted by concerns that randomly sequenced DNA sequences without assigned function would be patented. These concerns are reflected in Article 5(3) of the directive, which requires that the function of the DNA sequence be disclosed in the application upon filing so that its industrial applicability is known. The ECJ uses Recitals 23 and 24 out of their intended context and applies them to the interpretation of Article 9. In doing so, the ECJ ignores Recital 46, which provides the real concerns that formed the basis for Article 9: to prevent exhaustion of protection for self-reproducing living material after its first sale. Thus, the legislative purpose of Article 9 is actually to extend protection to progeny of the living material of the first sale, if the DNA sequence still performs its function in that progeny. There is no hint in Recital 46 or Article 9 of any limitation of protection, let alone a limitation to purpose-bound protection.

However, even if there are good reasons for disagreeing with the ECJ, its ruling is now a fact we will have to deal with. So what are the consequences? The bad news is that we no longer have absolute product protection for DNA sequences. We now have some form of purpose-bound protection for DNA sequences in that a sequence that is part of a non-viable material is no longer within the scope of protection of a

product claim on that DNA sequence. However, because the ECJ's judgment specifically refers to "circumstances such as those of the case in the main proceedings", it may arguably only apply to circumstances wherein the sequence is in dead material such as the soy meal. Living materials, e.g. harvested materials, wherein the sequence can still perform a function, even if it is silent, may still be protected. Another interesting question is how the ruling applies to isolated DNA sequences or to a composition comprising a DNA sequence that is a gene therapy vector, neither of which in that state can ever perform a biological function. The ECJ's ruling is not clear on this point. However, given that these situations are so different from the trace amounts of residual DNA in the soy meal, there is room to argue that the ruling would not apply to isolated DNA sequences or compositions with gene therapy vectors.

Now that Europe has lost absolute product protection for DNA sequences, it will be interesting to see how the US Federal Circuit will decide on the patentability and protection of DNA sequences without an indication of function on the Myriad Genetics BRCA1 and BRCA2 patents. ■

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