Expressed Sequence Tags: Any Prior Art Effect?

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Expressed sequence tags (ESTs)(1) represent nucleotide sequence information from a short segment (usually between 150 and 500 bp) of a randomly selected cDNA clone. The technology associated with generating ESTs pioneered by Dr. Craig Venter at the National Institutes of Health and the Institute for Genomic Research (TIGR) is described elsewhere. A well-publicized attempt by the NIH to patent ESTs sparked debate in both the scientific and the legal communities, resulting in a number of interesting patent law questions being raised, including whether ESTs meet the requirements of novelty, nonobviousness and practical utility (2) (see also <BLR 1256>, vol. 11, no. 1; <BLR 1284> through <BLR 1286> and <BLR 1298>, vol. 11, no. 2; <BLR 1313>, vol. 11, no. 3; <BLR 1334>, vol. 11, no. 4; <BLR 1358>, <BLR 1360>, and <BLR 1376>, vo. 11, no. 5; and <BLR 1386>, vol. 11, no. 6). Aside from the patentability of ESTs themselves, we believe an equally compelling issue is the prior art effect of published ESTs against later-discovered corresponding full-length genes and gene fragments.

The possibility that publicly available partial sequence information might render later-discovered corresponding full-length genes and gene fragments unpatentable was reported as a primary motive behind the NIH's decision to file Dr. Venter's EST application. Reid Adler, then director of the NIH Office of Technology Transfer, wrote at the time "[i]f everything goes into the public domain there is much less incentive to invest time and money developing a product. Our concern was to protect the invention early enough to give meaningful patent protection to companies that might seek a license from NIH." This was reiterated by the then director of the NIH, Dr. Bernadine Healy, who stated that "this was a major concern that led NIH to file for patents - namely, dumping sequence information on thousands of genes into the public domain might jeopardize later obtaining patents on the full gene or gene fragment with apparent function . . . attention to this issue should be the matter of some urgency [for Congress and the Administration]." At a Congressional hearing in September 1992, Venter went so far as to propose the following legislative change to the patent statute:

Prior art shall not preclude patentability of an amino acid sequence or nucleotide sequence solely because such prior art discloses a portion of such sequence.

Apparently, the NIH officials and Venter felt their concerns were justified, as claims directed to full coding portions of genes having between 400 and 500 base pairs were rejected by the U.S. Patent and Trademark Office as being obvious over the prior publication of homologous oligonucleotides having only 15 bp. The notion that prior publication of a short sequence of DNA renders an entire gene unpatentable has been furthered by at least one commentator:

Would the patent on ESTs make subsequent patent applications for full length cDNAs obvious under §103? The answer may be yes! Because the current skill in the art is sufficiently advanced, the use of a unique sequence of cDNA as a probe to identify the full-length cDNA may be obvious. Furthermore, even without patenting ESTs, so long as the sequences were published, the problem could exist. (7)

Technology has pushed rapidly forward in the time since the NIH applied for the first "EST patents" disclosing some 2,750 ESTs. Indeed, Dr. Venter and coworkers, drawing on TIGR data and the work of others, recently described 88,000 ESTs and assemblies of ESTs representing the partial sequences of almost 30,000 of the estimated 80,000 human genes. In view of this vast proliferation of nucleotide sequence information, the prior art effect of published ESTs against later-discovered corresponding full-length genes and gene fragments is an issue of significant importance to the biotechnology community. Thus, provided below is our analysis of this issue in view of recent opinions from the Court of Appeals for the Federal Circuit.
In *In re Bell* (991 F2d 781, 26 USPQ 2d 1529 [Fed. Cir. 1993]) and *In re Deuel* (51 F3d 1552, 34 USPQ2d 1210 [Fed. Cir. 1995]), the CAFC considered whether a full-length cDNA was obvious in view of the corresponding purified protein combined with a reference teaching a general method for isolating genes based on screening cDNA libraries with nucleotide probes, which are conventionally synthesized using information obtained from the protein's amino acid sequence. While admitting that "knowledge that some gene existed may have been clear," Judge Lourie, in writing for the majority, indicated that:

> the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.\(^9\)

Thus, in both *Bell* and *Deuel*, the nucleic acid compound claims were held nonobvious over the corresponding purified protein combined with a general method for isolating genes. Central to the analysis in each opinion was the view that genes and nucleic acids in general are chemical compounds, a position advanced previously by the CAFC in *Amgen v. Chugai*\(^10\) and *Fiers v. Sugano*.\(^11\)

This treatment of genes as chemical compounds is critical, as it renders the large body of preexisting chemical case law directly applicable to nucleic acid compound claims. In chemical patent practice, *prima facie* obviousness may be established by close structural similarity to a useful compound disclosed in the prior art. The rationale for finding *prima facie* obviousness is that in many instances, closely related compounds share properties that differ only to a degree that turns on structural similarity. As summarized by the court in *Deuel*:

*Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. Similarly, a known compound may suggest its analogs or isomers, either geometric isomers . . . or position isomers . . .*\(^12\)

Based on a structural similarity analysis, our question concerning the prior art effect of ESTs becomes a matter of determining whether an EST is sufficiently structurally similar to a corresponding full-length gene or gene fragment to render the claimed subject matter *prima facie* obvious. If the claimed gene or gene fragment does not have a close structural relation to the published EST; for example, is not an adjacent homolog, or an isomer, then one or more secondary references would be needed to establish obviousness.\(^13\) As indicated, the PTO has relied on secondary references describing general cloning methods as providing motivation to arrive at a claimed gene - an approach explicitly rejected by the CAFC in *Bell* and *Deuel*. Instead, the CAFC insisted that, for a *prima facie* obviousness rejection to be proper, the secondary references must establish motivation to make the precise structural modifications to the compound disclosed in the primary reference that would be necessary to arrive at the claimed nucleic acid.\(^14\) Thus, in our opinion, using secondary "method" references to establish motivation to arrive at a claimed full length gene or gene fragment from an EST disclosed in a primary reference would suffer the same defects as the obviousness rejections that were overturned in *Bell* and *Deuel*.

The following hypothetical is provided to illustrate our analysis. A patent application is filed with two claims, one directed to a full-length cDNA 2,000 nucleotides in length having a particular sequence and the other to the N-terminal 500 nucleotides that encode a biologically active polypeptide fragment. The examiner located on GenBank a published EST 400 nucleotides in length which was 100% homologous to nucleotides 50-450 of the claimed cDNA compound. Thus, the published EST covered 20% of the full-length cDNA and 80% of the N-terminal sequence. In this scenario, it is our opinion that both the full-length cDNA and the N-terminal fragment are nonobvious over the published EST. There is no structural similarity between the EST and either the full-length cDNA or its N-terminal fragment. By itself, the EST provides absolutely no suggestion as to the identity of the
remaining nucleotides that it does not overlap. In fact, until the claimed nucleic acid molecules were actually isolated and purified by the inventors, it would have been extremely unlikely for one of ordinary skill in the art to have contemplated the actual remaining sequence of what was ultimately obtained. As expounded by the court in Deuel, "[w]hat cannot be contemplated or conceived cannot be obvious." Thus, there would be no prima facie case of obviousness for either the full length gene or its N-terminal fragment.

We agree with others that the PTO may reject full-length genes and gene fragments over published ESTs on the basis that, once an EST is available, general methods are known for developing a nucleic acid probe capable of isolating the full-length gene and its fragments with a reasonable expectation of success. The PTO may also take the position that Bell and Deuel are distinguishable, as they deal with the patentability of nucleic acid compounds over published proteins and not published ESTs. However, in our opinion, such a narrow interpretation of Bell and Deuel would ignore, and in fact completely contradict, the rationale behind these decisions. As indicated, the basic premise underlying these cases is that DNA molecules are chemical compounds and must be treated as such when making patent law determinations - a view previously taken by the CAFC in Amgen and Fiers - while holding that there is no conception of a gene by availability of a method for isolating the gene unless the gene itself is defined in such a way as to distinguish it from other nucleic acid molecules. Thus, no matter what the fact scenario, analyzing claims directed to nucleic acid compounds according to traditional chemical patent law principles is by now a well-trodden path.

1. ESTs are also referred to in the biotechnology industry as "partial cDNA sequences."
9. Id., 51 F3d at 1559, 34 USPQ2d at 1215.
10. Amgen v. Chugai, 927 F2d 1200, 1206, 18 USPQ2d 1016, 1021 ("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it.").
11. Fiers v. Sugano, 984 F2d 1164, 1169, 25 USPQ2d 1601, 1604 (". . .irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility.").
12. Deuel, 51 F3d at 1558, 34 USPQ2d at 1214.

14. *Id.*, 51 F3d at 1558, 34 USPQ2d at 1215 (". . . the prior art does not disclose any relevant cDNA molecules, let alone close relatives of the specific, structurally-defined cDNA molecules of claims 5 and 7 that might render them obvious.").

15. *Id.*

16. In our opinion, an identical result would occur even for claims broader in scope, such as: "A nucleic acid molecule encoding a polypeptide having the amino acid sequence shown in SEQ ID NO 1." Such a claim reads on any nucleic acid molecule encoding the recited amino acid sequence. This notwithstanding, given the published EST as prior art, it still would have been extremely unlikely for one of ordinary skill in the art to have contemplated any of the remaining sequences (i.e., sequences not "covered" by the EST) encompassed by the claim. However, as pointed out by Goldstein & McConathy (Goldstein & McConathy, "Patent Applications On Partial cDNA Sequences," *THE JOURNAL OF NIH RESEARCH* 7:58, 60 (1995)), a different result would occur for claims reciting "and fragments thereof" - which generically read on any and all fragments of the gene including the prior art EST. Thus, to include "and fragments thereof" in a claim, we recommend also including a proviso explicitly omitting the EST to circumvent possible anticipation and obviousness rejections. (Relevant ESTs could be identified by an applicant prior to filing a patent application by searching GenBank.)

Arguably a determination of nonobviousness is also warranted as a matter of public policy as it allows full public dissemination of ESTs without precluding patents directed to later discovered corresponding full length genes and gene fragments. *Id.* Indeed, maintaining rejections over ESTs could result in human genome projects being shrouded in secrecy bringing about a wasted duplication of research efforts.

17. *Id.*

18. *Amgen*, 927 F2d at 1206, 18 USPQ2d at 1021.


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