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'Fisher' and Beyond: Issues for Patenting Expressed Sequence Tags

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The U.S. Court of Appeals for the Federal Circuit's decision in *In re Fisher,* 421 F3d 1365 (2005), has broad implications for the future of the biotech industry and the protection of drug and diagnostic discoveries based on the genetics revolution of the last decade.

At issue is a fundamental question covering the characterization and patentability of the prized products of that revolution—expressed sequence tags (ESTs). Are ESTs valuable research tools worthy of patent protection or are they merely emblematic of speculative research goals, which are not?

Patents for Expressed Sequence Tags?

In re Fisher highlights a biotechnology industry challenge—how to patent ESTs? In that case, the Federal Circuit affirmed the U.S. Patent and Trademark Office's (PTO) rejection of a patent application claiming purified nucleic acid sequences that encode proteins and protein fragments in maize plants. The court characterized Fisher's newly discovered ESTs as nothing more than "research intermediates" capable of helping scientists isolate protein-encoding genes to enable further experimentation and, accordingly, held that Fisher had failed to satisfy the "specific and substantial utility" requirement of 35 USC §101.

Despite its conclusion, the Federal Circuit was cognizant of the important role of ESTs in molecular genetics. The court recognized that complementary DNA (cDNA) libraries are useful to investigate gene expression, wherein at least one research goal is to understand gene expression insofar as it might enable scientists to regulate such expression and to control protein synthesis. As far as how ESTs contribute to this discovery, the court explained that:

> An EST is a short nucleotide sequence that represents a fragment of cDNA clone. It is typically generated by isolating a cDNA clone and sequencing a small number of nucleotides located at the end of one of the two cDNA strands. When an EST is introduced into a sample containing a mixture of DNA, the EST may hybridize with a portion of DNA. Such binding shows that the gene corresponding to the EST was being expressed at the time of mRNA extraction.

Are expressed sequence tags valuable research tools worthy of patent protection or mere emblems of speculative research goals, which are not? 'In re Fisher' has broad implications for the genetics revolution.

Fisher, represented by assignee Monsanto, asserted that the claimed ESTs were useful to:

(1) serve as a molecular marker for mapping the entire maize genome;

(2) measure the level of mRNA in a tissue sample;

(3) provide primers for polymerase chain reaction processes;

(4) identify polymorphisms;

(5) isolate promoters via chromosome walking;

(6) control protein expression; and

(7) locate genetic molecules of other plants and organisms.

'Specific, Substantial Utility'

The Federal Circuit applied the Supreme Court's *Brenner v. Manson,* 383 US 519, 534-35 (1966), test for a "specific and substantial utility" to Fisher's application. Under §101, a substantial utility requires "a significant and presently available benefit to the public" and a specific utility requires "a well-defined and particular benefit to the public." More specifically, Fisher needed to have "disclose[d] a use which is not so vague as to be meaningless."

The U.S. government argued exactly that—that Fisher's so-called inventions were "so general as to be meaningless." Amicus curiae offered their support for the government's contention. The amici proclaimed that Fisher's claimed uses amounted to "nothing more than a 'laundry list' of research plans, each general and speculative, none providing a specific and substantial benefit in currently available form." The Federal Circuit ultimately agreed with the government and amici, ruling that "none of Fisher's seven asserted uses meets the utility requirement of §101."

Of particular note, the Federal Circuit heeded the PTO's caution on the patentability of ESTs. The court approvingly pointed to a section within the PTO's 2001 Utility Examination Guidelines, 66 Fed. Reg. 1092-02 (Jan. 5, 2001), where the PTO cautioned against the general patentability of research intermediates:

> An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. [The PTO] must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

Using the "specific and substantial utility" standard and this precautionary approach as a backdrop, the court rejected Fisher's utility arguments, buttressing its conclusion with a citation to an example from the PTO's Manual of Patent Examining Procedure (MPEP). The example in MPEP §2107.1 asserts that, when claims are directed to polynucleotides used as gene probes or chromosome markers, the applicant must disclose a specific DNA target to satisfy §101. Thus, "the claimed ESTs, which do

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not correlate to an underlying gene of known function, fail to meet the standard for utility intended by Congress," meaning "the claimed ESTs have not been researched and understood to the point of providing an immediate, well-defined, real world benefit to the public meriting the grant of a patent."

The Dissent

Judge Randall R. Rader's dissent sheds light on the enormous potential impact of the Federal Circuit's decision. In concluding that Fisher's application claimed an invention that satisfied the utility requirement of §101, Judge Rader vehemently disagreed with the majority's dismissal of the claimed ESTs as mere research tools unworthy of patent protection. For, in Judge Rader's opinion, "if the claimed ESTs qualify as research tools, then they have a 'specific' and 'substantial' utility sufficient for §101."

Paradigmatically, the primary difference between the majority's and Judge Rader's reasoning is Judge Rader's acceptance of the claimed ESTs as analogous to a microscope that enables researchers to identify and understand otherwise unknown structures and functions. Therefore, according to Judge Rader, these ESTs provide an immediate, specific, societal benefit meritorious of patent protection. The majority, on the other hand, dismissed the microscope analogy as ostensibly appealing yet inherently flawed, noting that "a microscope has the specific benefit of optically magnifying an object to immediately reveal its structure." In their view, the claimed ESTs are limited in their usefulness only "to detect the presence of genetic material having the same structure as the EST itself," in turn providing no information about the underlying gene's overall structure or function. In essence, while Judge Rader saw the claimed ESTs as useful research tools, the majority found them to be merely speculative research goals.

Yet the PTO has granted EST patents, beginning with Incyte Pharmaceuticals' 1998 "Human Kinase Homologs" patent. An accurate count of these granted EST patents, however, is not easily ascertainable. The unavailability of data on pending and failed EST patent applications, furthermore, makes it difficult to determine why the PTO has allowed certain EST claims while denying others. Notably, it is not readily apparent how the utility associated with Fisher's claimed ESTs differs from that of previously issued EST patents. Seth Waxman, counsel to Fisher and former U.S. solicitor general, appears to propound the following explanation:

> The PTO effectively ceased granting patents on ESTs after it issued the 2001 Utility Guidelines.[1]

Legislative/Judicial Reversal?

Time will tell whether Congress—or the Federal Circuit itself—will allow the holding of *In re Fisher* to remain intact; a legislative or judicial reversal of *In re Fisher* would create a plethora of new controversies. Meanwhile, other important issues regarding the patentability of ESTs remain. First, assuming an EST claim meets the utility requirement of §101, applicants must still meet the enablement requirement of §112. Second, in cases in which ESTs are deemed patentable, courts will struggle with difficult issues in quantifying appropriate damages for the infringement of EST patents.

To be enabling under §112, a patent must provide disclosures sufficient to enable one skilled in the art to practice the invention commensurate with its claimed scope. This requirement ensures that the public receives sufficient information about the invention such that those skilled in the art can utilize it without undue experimentation. Unfortunately, *In re Fisher* sheds little light on the issue of EST enablement: The Federal Circuit merely noted that a claim that fails to meet the §101 utility requirement is ipso facto non-enabling under §112.

However, the Federal Circuit's §112 precedent indicates that the degree of specificity required for EST patentability will similarly challenge EST patent seekers. For example, in *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F2d 1200, 1213 (1991), the Federal Circuit ruled that for DNA sequences, where a patentee claimed all possible genetic sequences with a particular gene's activity, it was not sufficient to have made a gene and some analogs without clearly ascertaining their activity. The Federal Circuit confirmed and reinforced this position in *Fiers v. Revel*, 984 F2d 1164 (1993), holding that enablement "requires more than a mere statement that [DNA] is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself."

The value of an expressed sequence tags patent may depend on where courts perceive the "point of placement" of ESTs to be within the commercialization spectrum.

Damages

Litigation involving issued EST patents may be similarly controversial, as courts could have significant latitude in awarding patent infringement damages. In analyzing the value of an EST patent, courts are likely to consider the claimant's ESTs to be patented research tools. Since calculating the value of patented research tools in the drug development process has proved difficult, the quantification of damages due to the infringement of EST patents will be no less challenging.

An EST patentee will be, pursuant to 35 USC §284, entitled at the very least to damages in the form of "a reasonable royalty for the use made of the invention by the infringer." Recovery under the more valuable lost profits calculus is less likely, given the unlikelihood that the typical EST patentee will be able to prove that it would have made sales but for an infringement. Thus, courts will need to determine the royalty rate that a willing licensee would have paid to the patentee in a hypothetical arm's-length license negotiation that took place on the eve of infringement. In the context of drug development tools, *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F3d 860, 871 (Fed. Cir. 2003), sheds some light on this potentially difficult task:

> The value to a licensee of research tools lies, in part, in the point at which those tools are employed in the drug development continuum. A research tool enabling the identification of a drug candidate during high throughput screening, for instance, may supply more value to the ultimate invention than a research tool used to confirm an already recognized drug candidate's safety or efficacy.

Accordingly, the value of an EST patent may depend on where courts perceive the "point of placement" of ESTs to be within the commercialization spectrum. And, such damages could potentially be high if courts are willing to require infringers to pay "reach-through royalties" based on the infringer's sales of final commercialized products that resulted from discoveries that are merely facilitated in part by ESTs.

'SIBIA v. Cadus'

The jury verdict in *SIBIA Neurosciences, Inc. v. Cadus Pharmaceutical Corp.*, 1999 WL 33554682 (S.D. Cal. Feb. 26, 1999), rev'd on other grounds, 225 F3d 1349 (Fed. Cir. 2000), perhaps foreshadows the impact that reach-through royalties will have on the value of EST patents. In that case, SIBIA successfully asserted against Cadus its patent on a method for assaying compounds that exhibited agonist or antagonist activity. The jury awarded $18 million in damages based on Cadus' (and its research partners') expert testimony about future sales of new drug products that may be developed as a result of the infringing assays—but that haven't even been discovered. While the Federal Circuit never reached the damages issue on appeal, the trial judge let stand such a research tool reach-through royalty directed at nonexistent products that might be developed in the future. Questions remain as to whether such reach-through royalties constitute a "reasonable royalty" that EST patentees would be entitled to collect.

Conclusion

While it is not entirely certain what effect *In re Fisher* will have on the biotechnology community, one can safely assume that the case will not deter those rushing to the PTO to protect their EST discoveries. It is clear, however, that those potential patentees ought to focus just as much of their efforts on articulating the specific utility of their claimed ESTs as they expend discovering them.

1. William F. Lee et al., "Limits on Patentability in Life Sciences: Claims Covering Expressed Sequence Tags," 6 Sedona Conf. J. 95 (2005).