Federal Circuit Limits Patentability of Genetic Sequences

On April 3, 2009, the U.S. Court of Appeals for the Federal Circuit issued In re Kubin (Fed. Cir., No. 2008-1184), perhaps the most significant patent law decision affecting the genetic engineering industry in over a decade. At issue is the patentability of isolated genetic sequences, in this case encoding a previously identified, but unsequenced, protein.

Two Amgen scientists, Marek Z. Kubin and Raymond G. Goodwin, had invented a cDNA molecule encoding a natural killer cell activation inducing ligand (NAIL) protein involved in an immune response to tumors and viruses. The Federal Circuit held this invention to be obvious in view of knowledge of the protein's existence and commonly available cloning techniques for obtaining cDNA sequences. This decision criticized Federal Circuit precedent in cases, such as In re Deuel, 51 F.3d 1552 (Federal Circuit 1995), which had clearly established patentability of genetic sequences based upon the non-obviousness of the exact chemical structure of the nucleotide sequence, irrespective of the "routine" means by which the invention may be deduced.

The Kubin case also weakens the art-level distinction of biotechnology inventions generally, which previously were considered merely "obvious to try" but with frequently unpredictable, and hence patentable, experimental outcomes. The commercial significance of this case is highlighted by the number of amicus briefs filed by entities such as Eli Lilly & Co., Amylin Pharmaceuticals Inc., Johnson & Johnson, Novartis, GlaxoSmithKline and the Biotechnology Industry Organization, in support of Amgen’s position of patentability. Given the momentum for passage of pending legislation for FDA approval of generic and follow-on biologics, the stakes have never been higher for changing the standard for obviousness of genetic sequence patent claims.

Recent Obviousness Developments Preceding Kubin

The Federal Circuit in Kubin was profoundly influenced by the U.S. Supreme Court’s recent obviousness pronouncements in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007) and the implications for inventions which may be "obvious to try" and result in an expected outcome. In KSR, the Supreme Court rejected a rigid application of the "teaching, suggestion, or motivation" test and mandated an expansive and flexible approach to determine whether a patent is obvious under 35 U.S.C. §103 of the Patent Act. The Supreme Court stated that an invention may be obvious when there is market pressure to solve a problem and when there are a finite number of identified, predictable solutions, so that a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, according to the Court, it is likely not the product of innovation but of ordinary skill and common sense.

However, the invention in KSR did not concern biotechnology, but rather was directed to a mechanical device, i.e., a computer-controlled automobile accelerator system with an electronic sensor on the accelerator pedal support. The Court's "obvious to try" and "predictable result" approach is a workable rationale for addressing the obviousness of combining known physical components to produce a device with predictable features. However, at issue in the patentability or obviousness of claimed genetic sequences is the very nature of the predictability of the result. While it may well be predictable that an accurate nucleic acid structure will result from a particular sequencing methodology, the resulting chemical structure itself (i.e., the cDNA sequence) still cannot be predicted a priori. Moreover, the
Federal Circuit had previously recognized that biotechnology is an “unpredictable” art, and that most often the problems addressed in molecular biology do not have predictable solutions.

Federal Circuit Precedent for Patenting Genes

The Federal Circuit’s ruling in Kubin was a marked departure from settled law controlling the obviousness standard for patenting genes. In a highly analogous case, In re Bell, 991 F.2d 781 (Fed. Cir. 1993), the Federal Circuit ruled that claims directed to nucleic acids encoding human insulin-like growth factors were not obvious, even though the amino acid sequences for such human insulin-like growth factors were disclosed in the prior art, as well as the general methods for isolating a gene by using degenerate probes corresponding to short amino acid sequences of the known protein.

The Federal Circuit in Bell reasoned that due to the degeneracy of the genetic code, the amino acid sequences for the known growth factors could be coded by more than $10^{36}$ different nucleotide sequences, only a very few of which were deduced and being claimed. Therefore, given the nearly infinite number of sequence possibilities, and the failure of the cited prior art to suggest which of those possibilities was the claimed human sequence, the claimed cDNA sequence was held not to be obvious. Importantly, the Federal Circuit in Bell distinguished patentability of a claimed composition from a method, stating that the issue is the obviousness of the claimed compositions, not of the method by which they are made. Clearly, the patentability of a product does not depend on its method of production, consistent with the statutory limitation under 35 U.S.C. §103(a) that “[P]atentability shall not be negatived by the manner in which the invention was made.”

Following Bell, in Deuel, the claims at issue were directed to isolated DNA molecules encoding heparin-binding growth factors. The Federal Circuit in Deuel ruled that a combination of a reference disclosing a partial amino acid sequence of the protein, together with a prior art reference teaching a method of gene cloning, does not render the claims directed to cDNA molecules encoding the protein obvious. In Deuel, the Federal Circuit considered the claimed DNA sequences as “new chemical entities in structural terms.” Accordingly, the Federal Circuit concluded that the obviousness rejection based on the alleged obviousness of a method of making such molecules, not the obviousness of the structurally similar molecules themselves, is improper. In the wake of the Kubin case, however, the reasoning in Deuel and Bell can no longer be relied upon.

The Kubin case

Kubin is a pivotal post-KSR obviousness case addressing the classical biotechnology invention involving the cloning and characterization of a human gene encoding a partially isolated, but not yet sequenced, protein. The human NAIL protein was known to exist on the surface of natural killer (NK) cells and to be capable of binding to the CD48 protein expressed on the surface of other cells to elicit an immune response against certain viruses and tumors. Using a cDNA expression library generated from pooled mRNAs extracted from human NK cells stimulated with known activators, and an available antibody to the murine version of the protein, Kubin and Goodwin were able to isolate and clone the human NAIL cDNA, and became the first to sequence both the cDNA and amino acid sequences of the human NAIL protein.

The claimed subject matter in Kubin is reflected in representative independent claim 73 directed to “an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.” Therefore, the claims in Kubin are directed to a genus of isolated nucleic acid molecules encompassing an extracellular binding domain of the NAIL protein that binds to CD48.
The claims at issue were held invalid as obvious under 35 U.S.C. §103(a), and for lack of enablement and failure to meet the written description requirement under 35 U.S.C. §112, 1st paragraph. The Federal Circuit only discussed the obviousness aspects of the invention. The Federal Circuit did not address many issues of fact regarding undefined expression and cloning parameters in the prior art that were necessarily elucidated in order to reveal the cDNA sequence.

Relying on KSR, Judge Randall R. Rader eliminated the effective non-obviousness presumption biotechnology has enjoyed as an unpredictable art. In writing for the Federal Circuit, he stated that “this court cannot deem irrelevant the ease and predictability of cloning the gene that codes for that protein. This court cannot, in the face of KSR, cling to formalistic rules for obviousness, customize its legal tests for specific scientific fields in ways that deem entire classes of prior art teachings irrelevant, or discount the significant abilities of artisans of ordinary skill in an advanced area of art.”

Rader further stated that KSR limits the Federal Circuit’s reliance on Deuel. “Insofar as Deuel implies the obviousness inquiry cannot consider that the combination of the claim’s constituent elements was ‘obvious to try,’ the Supreme Court in KSR unambiguously discredited that holding,” Rader said. With respect to the proper use of the “obvious to try” standard, Rader noted that the Supreme Court’s admonition against such a formalistic approach to obviousness “actually resurrects this court’s own wisdom in” In re O’Farrell, 853 F. 2d 894 (Fed. Cir. 1988).

O’Farrell acknowledged that the “obvious to try” standard can be erroneously equated with obviousness in two situations. As re-stated in Kubin, the first situation where an invention might be argued to be “obvious to try,” but the lack of predictability of the result mitigates against obviousness is “where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities.” This was contrasted with KSR obviousness “where a skilled artisan merely pursues ‘known options’ from a ‘finite number of identified, predictable solutions.’ ”

The second remaining non-obviousness situation, where “obvious to try” does not mitigate toward ultimate obviousness, is when the “obvious to try” was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. Again, Kubin indicated that KSR affirmed the inverse of this statement by stating that an invention is obvious unless “the improvement is more than the predictable use of prior art elements according to their established functions.”

Rader found that neither of the two “obvious to try pitfalls” applied in the Kubin case, concluding that “the record shows that a skilled artisan would have had a resoundingly ‘reasonable expectation of success’ in deriving the claimed invention in light of the teachings of the prior art.” The Federal Circuit acknowledged that the Kubin and Goodwin invention was “some minor advance in the art,” but that “[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress.”

Kubin’s Impact on Gene Patenting

The Federal Circuit’s decision in Kubin generally means that to the extent a protein has been previously identified, its nucleotide sequence is no longer patentable. The broader application of Kubin will include attempts to reject or invalidate claims directed to biotech inventions which claim an outcome of experimentation from among a range of expected results, even though not expressly predictable. There will undoubtedly be an increase in invalidity challenges to existing gene patents by those seeking to market generic and follow-on biologics prior to patent expiration, in view of the likelihood that pending regulatory legislation also passes. Clearly, the patentability standard for gene sequences and the commercial exclusivity available for such biotech inventions have been dramatically altered by the
Federal Circuit’s *In re Kubin* decision.

If you have any questions regarding this Legal Alert, please feel free to contact any of the attorneys listed below or the Sutherland attorney with whom you regularly work.

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