A nail in the coffin for DNA sequence patents?

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Does the recent Board decision in *Ex parte Kubin* mean the end for biotech patents claiming DNA sequences?

Imagine the following scenario: a university researcher publishes a paper describing the isolation and characterization of a protein having a commercially desirable biological activity; a biotech company then clones the cDNA for the desirable protein, characterizes the cloned sequences and submits a patent application claiming a nucleic acid molecule encoding the amino acid sequence of the desirable protein. Until recently, the company could look forward to obtaining a patent for the claimed polynucleotide. However, this expectation is now upset by the recent Board of Patent Appeals and Interferences decision in *Ex parte Kubin*[1].

The Kubin and Goodwin application

The patent application of Kubin and Goodwin (application no. 09/667,859) included claims to nucleic acids encoding natural killer (NK) cell activation inducing ligand (NAIL), a membrane protein found on human NK cells[2]. The claims at issue were represented by claim 73 of the application: 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.

The United States Patent and Trademark Office (USPTO) cited three references particularly relevant to claim 73:

(i) A patent to Valiante *et al.*[3], which describes human cell surface antigen p38 and a monoclonal antibody that binds the antigen. The patent provides a theoretical example of how the monoclonal antibody might be used to clone p38 by panning, but does not describe any p38 clone, any isolated p38 protein or any p38 nucleotide or amino acid sequence. It turns out that the NAIL protein of Kubin and Goodwin is the same protein as p38.

(ii) The Sambrook *et al.* manual *Molecular Cloning: A Laboratory Manual*[4].

(iii) An article by Mathew *et al.* describing the cloning and characterization of the mouse 2B4 gene product, which is the mouse homolog of human NAIL[5].

The USPTO rejected claim 73 and related claims as obvious based on the three references, and the Board upheld the obviousness rejection. According to the Board, a person of ordinary skill in the art would have had a reasonable likelihood of success in cloning NAIL by following the theoretical example of Valiante *et al.* and using conventional procedures as described in the Sambrook *et al.* and Mathew *et al.* references. Thus, the Board found that the claims to nucleic acids encoding NAIL were obvious.

The *Deuel* precedent

The Board's decision is at odds with the obviousness standard set out by the Court of Appeals for the Federal Circuit, the principal reviewing court for the Board. In the 1995 decision *In re Deuel*[6], the Federal Circuit reasoned that obvious methods of isolating a DNA molecule say nothing about the DNA molecule's nucleotide sequence. As such, the Federal Circuit decided that known methods of isolating a DNA molecule do not preclude claims to the DNA molecule itself.

The Federal Circuit's rationale is directly applicable to the NAIL claims in the Kubin and Goodwin application. Although the theoretical example of Valiante *et al.* and the conventional procedures described in the Sambrook *et al.* and Mathew *et al.* references may have been obvious ways to isolate a NAIL clone, they say nothing about the nucleotide sequence of the clone. Moreover, none of the references provided any NAIL amino acid or nucleotide sequences, or even described the isolation of the NAIL protein. Thus, under *Deuel*, claim 73 and the related NAIL claims should not have been rejected for obviousness.

How did the Board in *Ex parte Kubin* overcome the Federal Circuit's prior holding in *In re Deuel*? With sleight of hand, the Board said that the Federal Circuit's decision was no longer controlling due to the increased level of skill in the art that had been attained since the *Deuel* decision, and the factual differences between the *Kubin* and *Deuel* cases. Unfortunately, the Board did not identify the particular increases in the level of skill, or point to relevant factual differences. The Board did note, however, that the recent Supreme Court decision in *KSR International, Co. v. Teleflex Inc.*[7,8] appeared to weaken the *Deuel* decision under an "obvious to try" rationale.

KSR's "obvious to try" analysis

According to the Board, the reasoning the Supreme Court applied in *KSR* was also applicable to the NAIL claims. In *KSR*, the claim at issue was directed to a mechanical device—a vehicle pedal assembly having an electronic sensor for detecting pedal position. In commenting on whether a patent claim could be proved obvious merely by showing that a combination of claim elements was "obvious to try," the Supreme Court said that when there is a need to solve a problem, and there are a finite number of identified and predictable solutions to a problem, there is good reason to pursue the known options. If this pursuit leads to the anticipated success, the success was likely the product of ordinary skill and common sense. In such a case, the fact that the combination of claim elements was obvious to try might show that the combination was obvious. Applying the *KSR* reasoning to the NAIL claims, the Board decided that the problem was isolating a NAIL cDNA, and that a

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limited number of methods were available to do so. Also, there was a reasonable expectation that at least one of the methods would be successful. Therefore, isolating NAIL cDNA was the product of ordinary skill and common sense, not of innovation. Thus, according to the Board, the NAIL claims were obvious.

In analyzing the NAIL claims, the Board took liberties in applying the *KSR* rationale. In *KSR*, the Supreme Court applied the obvious-to-try rationale to the components of the claim. In contrast, what was obvious to try in the Board's analysis were various cloning methods. Although this might mean that a method of cloning would be obvious, the NAIL claims were not directed to a method of cloning—they were directed to chemical compositions, that is, polynucleotides having particular sequences. The Board's reasoning seems to stretch the scope of the *KSR* decision by applying the obvious-to-try rationale to unclaimed cloning methods rather than to the polynucleotide components of the claims.

Implications for DNA claims

To recap, the Board in *Ex parte Kubin* decided that the NAIL claims were obvious in light of a disclosure of NAIL protein and a description of how to isolate a NAIL cDNA using standard techniques. The decision of the Board is now under appeal at the Court of Appeals for the Federal Circuit. However, unless and until the decision is overturned by the Federal Circuit, the Board's decision is precedential and therefore must be followed by the Board and USPTO examiners. Indeed, in recently published examination guidelines[9] for determining obviousness, which the USPTO issued in light of the *KSR* decision, *Ex parte Kubin* is cited as an appropriate example of the obvious-to-try rationale.

At least for applications filed after the Kubin and Goodwin application (that is, September 20, 2000), the *Kubin* decision will make it harder to obtain claims to a polynucleotide encoding a protein when that encoded protein is already known. This applies even if the protein has not been purified. For example, in *Kubin* itself, NAIL had not been purified by Valiante *et al.* and was identified only by its interaction with a monoclonal antibody.

The *Kubin* decision also has an impact on issued patents. Because *Kubin* changes the way a patent examiner views and applies the prior art, DNA patents will be ripe for reexamination, a procedure in which the USPTO reevaluates the validity of claims in an issued patent. During reexamination, the claims are examined as if they were being presented in a patent application. For DNA patents where an encoded protein was already known at the time the application was filed, *Kubin* will make it harder for nucleic acid claims to survive the reexamination process because the examiner can now reject the claims based on the known protein and standard cloning techniques.

Is there a way to respond to a claim rejection based on *Ex parte Kubin*? One way was suggested in the *KSR* decision. In *KSR*, the Supreme Court noted that a combination of known components that yields unpredictable results is an indication of nonobviousness. Because knowledge of a protein and ways of cloning it does not predict the actual nucleotide sequence and derived amino acid sequence of a nucleic acid molecule encoding the protein, a patent applicant could argue that the nucleotide and amino acid sequences are unpredictable, nonobvious results of the cloning methods. Whether the USPTO will give credence to such an argument remains to be seen.

The Board's decision in *Ex parte Kubin* conflicts with the Federal Circuit's decision in *In re Deuel*. Unless the Board's decision is overruled by the Federal Circuit, *Ex parte Kubin* spells trouble for those claiming DNA sequences.

1. *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007).
2. Kubin, *et al. Eur. J. Immunol.* **29**, 3466–3477 (1999).
3. US Patent No. 5,688,690 (1997).
4. Sambrook, J., Fritsch, E. & Maniatis, T. *Molecular Cloning: A Laboratory Manual*, edn. 2 (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).
5. Mathew, P.A. *et al. J. Immunol.* **151**, 5328–5337 (1993).
6. *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).
7. *KSR International Co. v. Teleflex Inc.*, 550 U.S.___, 127 S.Ct. 1727 (2007).
8. Teitelbaum, R. & Cohen, M. *Nat. Biotechnol.* **25**, 1105–1106 (2007).
9. *Federal Register* **72**, 57526–57535 (2007).