Research Discoveries after Kubin

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Introduction

In re Kubin, decided by the U.S. Court of Appeals for the Federal Circuit on April 3, 2009, substitutes the old rule on awarding patents for DNA research with a new one.[1] Specifically, the existence of a general method of isolating DNA molecules is now relevant to the question of whether the DNA molecules themselves would have been obvious under 35 U.S.C. § 103. With the commercialization of biomedical discoveries made at academic or basic research centers being highly dependent upon patents to protect the substantial investment of risk capital for product development, will this new rule adversely affect those technologies based upon DNA—technologies at the forefront of today's molecular medicine?

Patent Primer for DNA Inventions

One of the judges of the three-judge panel that decided *Kubin* sensibly requested the advocates during oral argument to state their positions in a way that he could understand because he humbly admitted that he lacked a scientific background. Introductions on patent law, technology transfer, and biological science are provided to assist those, who, like the judge, lack a certain background. These tutorials are helpful as a basis for understanding the full impact of *Kubin*.

Let us begin with a patent primer and first examine some basics that apply to all inventions coming from many biomedical research programs. To start: A patent protects an

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invention or discovery by giving its owner the right to exclude others from its use. Generally, the term of a new patent is 20 years from the date on which the application for the patent was filed in the United States. The Constitution of the United States sets forth the reasons for patenting in Article I, Section 8, by giving Congress the power "to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries."

Under this power Congress enacted the first patent law in 1790, with the most recent patent law being reenacted in 1952. The patent laws are now codified in Title 35 of the United States Code. The operative words from the Constitution, of course, are *limited* and *right* or temporary monopoly. The Constitution authorizes these awards of a temporary monopoly to inventors for their discoveries to promote the progress of the useful arts, of which the development of new drugs and medicines is certainly one.

DiMasi et al. estimated the average cost of new drug development, including unsuccessful products and financial opportunity costs.[2] This publication determined that the average research and development (R&D) cost per new drug, from concept to U.S. Food and Drug Administration (FDA) approval, is 802 million in year 2000 dollars.

Take, for example, the case of thyroid-stimulating hormone (TSH).[3] Many valuable proteins occur in nature only in minute quantities or are difficult to purify from natural sources. The availability of substantially pure TSH now makes the diagnosis and treatment of human thyroid cancer a reality. Previously, the only available method to diagnose and treat human thyroid cancer involved administering TSH to stimulate the uptake of radioactive iodine into the cancer. Such stimulation was used as a diagnostic test to localize the tumor by scanning and was subsequently used to treat the cancer by giving large doses of radioactive iodine to kill the cancer. All of the diagnostic tests and therapies depended upon high levels of human TSH.

However, there was not enough natural product available from human pituitaries collected at autopsies. Furthermore, even if available, the human pituitaries had been found to be contaminated with viruses. As a result, the regulatory authorities had forbidden the use of the natural product for any human diagnostic or therapeutic studies.

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The diagnosis and treatment of thyroid cancer now involves cloning the gene for TSH and using it to make *recombinant* TSH. Recombinant TSH means making TSH by cloning the gene. TSH is now available in large quantities and is uncontaminated with viruses or other byproducts of collecting human pituitaries from autopsies. The recombinant TSH is used to achieve maximal uptake of radioactive iodine into the tumor for both diagnosis and treatment.

Although the exact cost of bringing this specific treatment from concept all the way to FDA approval has not been disclosed, a figure anywhere near the DiMasi et al. estimated average would represent a significant investment and substantial risk of capital. By virtue of the temporary monopoly, patents let companies at least recoup the high cost of R&D, thus giving companies an incentive to invest in new drugs and laboratory tests.

What in the way of DNA-related inventions can be patented? You cannot patent an idea, but rather a practical application of that idea. In the language of the statute, anyone who "invents or discovers" a "process, machine, manufacture, or composition of matter" or "improvement thereof" may obtain a patent. These statutory classes of subject matter taken together include, in the words of the legislative history of the 1952 Patent Act, "anything under the sun that is made by man," plus processes for making the products. Accordingly, subject matter of DNA inventions would typically be eligible for patent protection if it is made by man, i.e., if it is manmade, as opposed to being simply a product of nature.

Products of nature cannot be patented because they are not "made by man." Nevertheless, we can patent natural substances, provided that they are "isolated and purified," because they do not occur in that form in nature. U.S. Patent No. 4,703,008, a representative patent, is directed to a purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin (EPO). EPO is a drug that increases red blood cells. It is prescribed to patients with cancer undergoing chemotherapy, because the chemotherapy tends to cause the red blood cells of the patients to decrease thus making the patients who are already suffering from cancer anemic and weak. The EPO restores the red blood cells to normal.

The United States Patent and Trademark Office (USPTO) takes the position that an isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is

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eligible for a patent because that DNA molecule does not occur in that purified or isolated form in nature.[4] EPO is one such gene. Accordingly, you cannot patent a gene per se that is present in a human body, only an "isolated and purified" gene in a test tube.

The steps for obtaining a patent for a DNA invention require describing the invention in a patent application, including teaching how to make and use the invention (formal requirements). But to meet the substantive conditions for patentability, an invention must also be novel and nonobvious. Novelty means the invention must be *new* (i.e., original), as well as not being precluded from patenting by what is defined in the patent law as a "statutory bar." For example, an invention cannot be patented if the invention is publicly disclosed (such as by publication of a manuscript) or commercialized (such as by offer for sale). The U.S. provides a grace period of one year before such statutory bars come into play.

Even if the subject matter sought to be patented is novel and involves one or more differences from the prior art, a patent may still be refused if the differences would be obvious. In other words, the subject matter sought to be patented must be sufficiently different from what has come before to a person having ordinary skill in the art to be nonobvious. For example, in the original obviousness case decided by the Supreme Court of the United States in 1850, the substitution of porcelain for wood to make a doorknob was deemed to be unpatentable.[5] The prior art was a wood doorknob. Even though the porcelain doorknob invention was novel in view of this prior art doorknob, it was nevertheless unpatentable because it would have been obvious to substitute porcelain for wood in a doorknob.

Patenting and Licensing DNA Inventions from Basic Research Programs

In general terms, DNA inventions (perhaps more appropriately termed as genomic inventions) arising from basic research programs can be thought to include a wide variety of technologies and materials: cDNAs, expressed sequence tags, haplotypes, antisense molecules, small interfering RNAs, full-length genes, etc.[6] The commercial use of these sequences can involve nucleic acid-based diagnostics, potential gene therapy applications, the development of new DNA and RNA, as well as the expression products themselves—the basis for the founding of the biotechnology industry.

Patenting and technology commercialization programs (such as licensing) at basic research organizations provide a means for getting new DNA inventions to the market for

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public use and benefit. With this public and commercial use of DNA inventions often comes new recognition of the value of basic research programs to the university or other organization that originated it. These inventions also serve as a helpful means to attract new R&D resources and partnerships to the laboratory. Through licensing or other technology transfer means, there is thus a return on investment whether that is measured in terms of financial, educational, or societal parameters or some combination thereof. Finally, there is an economic development aspect to the commercialization of DNA inventions via new job and company formation for the sale and delivery of innovative products.

A substantial portion of the DNA inventions that occurring at basic research programs arises from research that is federally funded. The Bayh-Dole Act of 1980[7] allows such grantees and contractors to retain ownership in subject inventions made using federal funds, seek patent protection on these inventions, and license these inventions with the goal of promoting their utilization, commercialization, and public availability. In 1986, federal laboratories were given a statutory mandate under the Federal Technology Transfer Act[8] and Executive Order 12591 to ensure that new technologies developed in federal laboratories were transferred to the private sector and commercialized.

Commercialization of DNA inventions from nonprofit basic research institutions typically follows a multistep process as academic and federal laboratories typically do not provide, nor have the means to provide, commercialization of the technology themselves. A contractual agreement (typically a license) is created to give permission to use DNA patents, materials, or assets to bring a product concept to market. Financial consideration or other benefits are received by the research institution in exchange through what is often an agreement with a small company that will bring in a large corporate partner later in development.

Patent and Licensing Practices for DNA Inventions

Thus for research institutions, commercial applications or reasonable expectations of commercial applications are the key driver in determining how to effectively handle patenting and licensing of DNA inventions. However, explicit commercial applications are not always clear at the early development stages for such inventions. At the early stages

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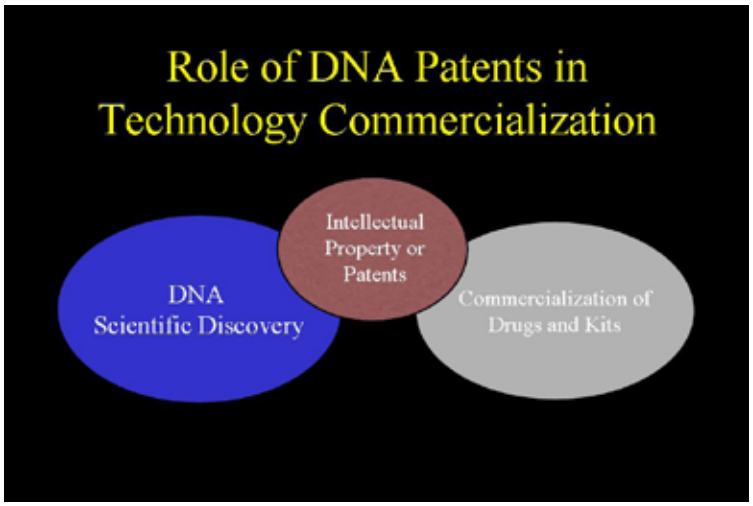
of this process, patent protection for DNA inventions is generally sought when significant further R&D by the private sector is required to bring the invention to market, such as in the examples of TSH and EPO previously described and shown in a general nature in Figure 1.

Figure 1: Role of DNA Patents in Technology Commercialization



In contrast, when significant research and development are not required for DNA inventions, patent protection is likely not needed—such as is often the case for research materials and research tool applications. For example, for a DNA invention where publication alone is sufficient for dissemination and commercialization, patent protection may be an unnecessary expense and not valued by licensees. When patent protection is obtained, it is possible for basic research institutions to discern those applications that absolutely require exclusive licensing to attract investment and risk capital from those that may not.

The Invention: DNA Encoding the Protein NAIL

Given the importance of patents and licensing to achieve commercialization of DNA inventions, what is the impact of *Kubin* on basic research institutions? The invention claimed in the 1999 patent application, naming *Kubin* and Goodwin as inventors, was related to cloned and sequenced DNA encoding the protein NAIL (*n*atural killer-cell *a*ctivation *i*nducing *l*igand). NAIL is useful for regulation of the immune response. Figure 2 illustrates the protein sequence (discussed below) of NAIL.[9] The sequence for NAIL goes from 1 to 365 and reads as depicted in Figure 2.

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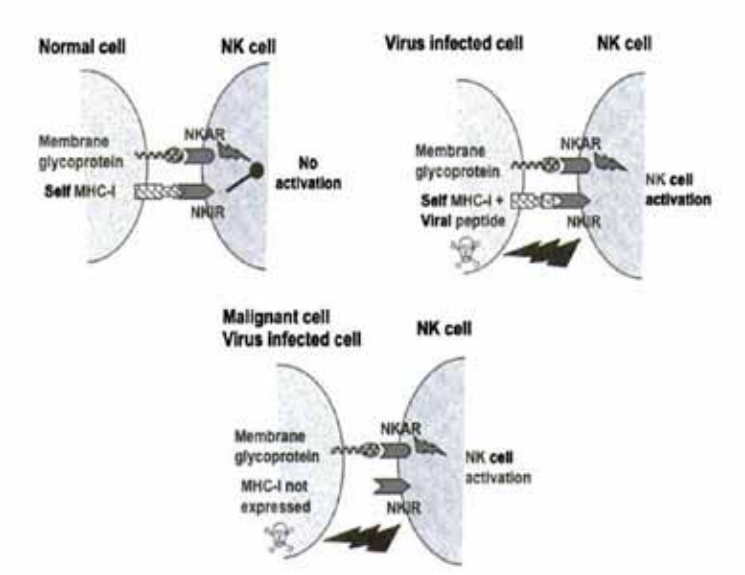
Figure 2: The Kubin *Invention: DNA Encoding the Protein NAIL*

```
  1  MLGQVVTLIL LLLLKVYQGK GCQGSADHVV SISGVPLQLQ PNSIQTKVDS
 51  IAWKKLLPSQ NGFHHILKWE NGSLPSNTSN DRFSFIVKNL SLLIKAAQQQ
101  DSGLYCLEVT SISGKVQTAT FQVFVFDKVE KPRLQGQGKI LDRGRCQVAL
151  SCLVSRDGNV SYAWYRGSKL IQTAGNLTYL DEEVDINGTH TYTCNVSNPV
201  SWESHTLNLT QDCQNAHQEF RFWPFLVIIV ILSALFLGTL ACFCVWRRKR
251  KEKQSETSPK EFLTIYEDVK DLKTRRNHEQ EQTFPGGGST IYSMIQSQSS
301  APTSQEPAYT LYSLIQPSRK SGSRKRNHSP SFNSTIYEVI GKSQPKAQNP
351  ARLSRKELEN FDVYS    (SEQ ID NO:2)
```

Turning to biology, Figure 3 illustrates the mechanism of target cell recognition by natural killer (NK) cells.[10] The activation or lack of activation of cell-killing pathways depends upon the balance between activating receptors (NKAR, which interacts with cellular glycoproteins) and inhibitory receptors (NKIR, which interacts with self-major histocompatibility complex MHC-1 molecules). If the inhibitory receptor is not triggered (due to either lack of interaction of the inhibitory receptor with MHC-1 self molecules or lack of expression of MHC-1 molecules on the cell membrane), stimulatory activity prevails and the target cell is killed.

Figure 3: Mechanism of Target Cell Recognition by Natural Killer Cells



Adapted/reproduced from Virginia M. Litwin (2007). Originally published in Medical Immunology. *Refer to Note 10.*

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The first panel of Figure 3 illustrates no activation. Here, in the normal cell, the inhibitory receptor is triggered (due to both interaction of the NKIR inhibitory receptor with self MHC-1 molecules and expression of MHC-1 molecules on the cell membrane), thus the cell-killing pathway is not activated.

The second panel of Figure 3 illustrates NK cell activation by a virus-infected cell. Here, in the virus-infected cell, the inhibitory receptor is not triggered (due to lack of interaction of the NKIR inhibitory receptor with self MHC-1 molecules), thus stimulatory activity prevails and the target cell is killed, depicted by the skull and crossbones symbol.

The third panel of Figure 3 illustrates NK cell activation by a malignant cell. Here, in the malignant cell, the inhibitory receptor is not triggered (due to lack of expression of MHC-1 molecules on the cell membrane), thus stimulatory activity prevails and the target cell is killed, depicted, again, by the skull and crossbones symbol.

Putting it all together, the *Kubin* invention is related to a NKAR activating receptor, called NAIL, which interacts with a membrane glycoprotein, called CD48. NAIL maintains a balance with a NKIR inhibitory receptor, which interacts with a MHC-1 like-ligand. NAIL kills target cells that are virus-infected or malignant due to lack of interaction of NKIR and ligand (skull and crossbones).

Concluding with the science of DNA, Figure 4 illustrates the central dogma of molecular biology.[11] According to the dogma, and as depicted in the living cell illustrated in Figure 4, DNA is made into RNA, and RNA is made into protein. DNA is short for deoxyribonucleic acid, RNA is short for ribonucleic acid, and protein, of course, is the basic building block of all living cells. The terms *gene* and *DNA* are used interchangeably, because a gene is a piece of DNA. Accordingly, one gene makes one protein. Referring to the amino acid chain in Figure 4, a protein, by definition, is a chain of amino acids.

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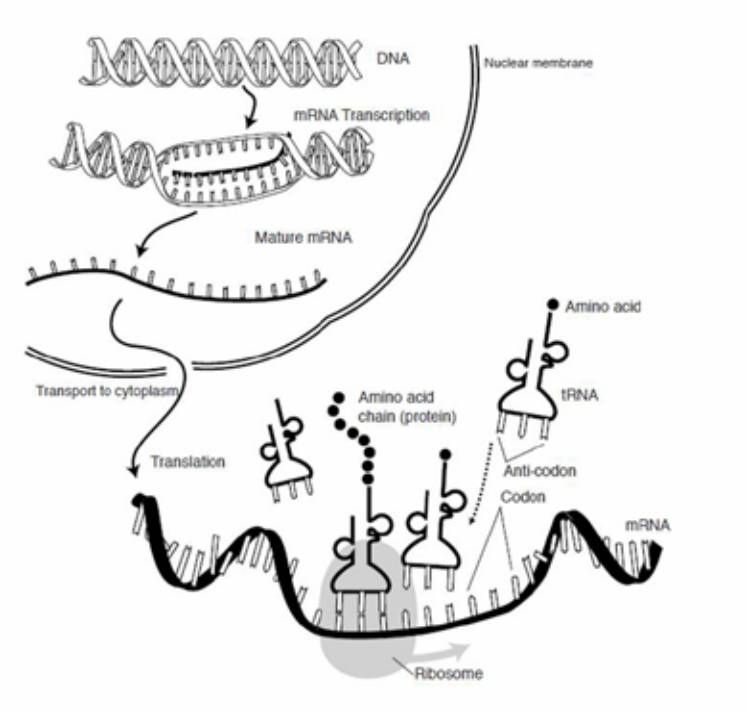
Figure 4: The Central Dogma of Molecular Biology = DNA → RNA → Protein.



There are a total of 20 separate naturally occurring amino acids. Any standard textbook lists the amino acids and provides their three-letter and one-letter abbreviations. Each type of protein has a unique sequence of amino acids, and there are thousands of different proteins, each with its own particular amino acid sequence. You can deduce the protein sequence from the DNA sequence. You cannot, however, deduce the natural DNA sequence from the protein sequence (due to redundancy of the genetic code, i.e., more than one triplet of DNA bases can encode the same amino acid).

Returning now to Figure 2, it illustrates the amino acid sequence of NAIL. The sequence is 365 amino acids long. The first amino acid in this sequence reads M, which stands for methionine, with the three-letter abbreviation being Met and the one letter abbreviation being M. Next in the sequence comes L, which stands for leucine, with the three-letter abbreviation being Leu, and the one-letter abbreviation being L. Then comes G in the sequence, which stands for glycine, with the three-letter abbreviation being Gly, and the one-letter abbreviation being G. Using these first three amino acids as illustrations, you can now understand the order, or sequence, of amino acids in NAIL.

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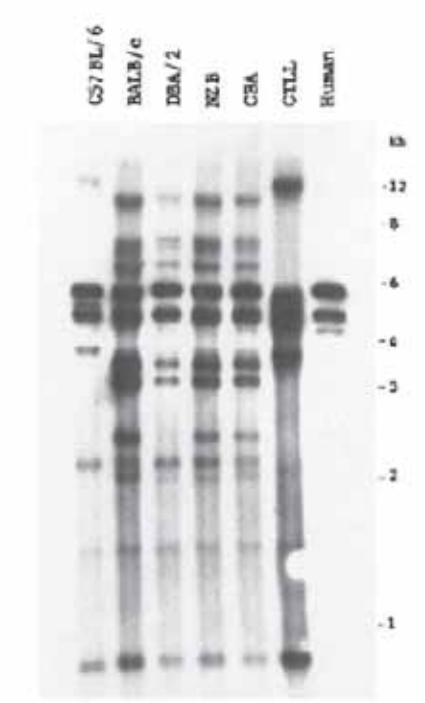
The Prior Art: Maniatis Laboratory Manual and a Protein Band on a Gel

The first of three pieces of prior art in the *Kubin* case was *Molecular Cloning: A Laboratory Manual* by Sambrook, Fritsch, and Maniatis (2d ed. 1989).[12] This is the Maniatis laboratory manual, so-called for the last named author. It is considered by many to be a cookbook for cloning genes.

The second piece of prior art was Mathew et al., *J. Immunol.* 151 (1993): 5328-5337 (Mathew article), as illustrated by the representative drawing reproduced in Figure 5.[13] The prior discovery in the Mathew article was related to a NKAR activating receptor in the mouse, called 2B4. The mouse 2B4 gene was cloned and sequenced. The genomic DNA blot analysis shown in Figure 5 identified a human homologue, or counterpart, of the mouse 2B4 gene (lane "human").[14] The human homologue turned out to be NAIL, but the gene was split (two bands) and was neither cloned nor sequenced.

Figure 5: The Kubin *Prior Art: Mathew Article (1993)*



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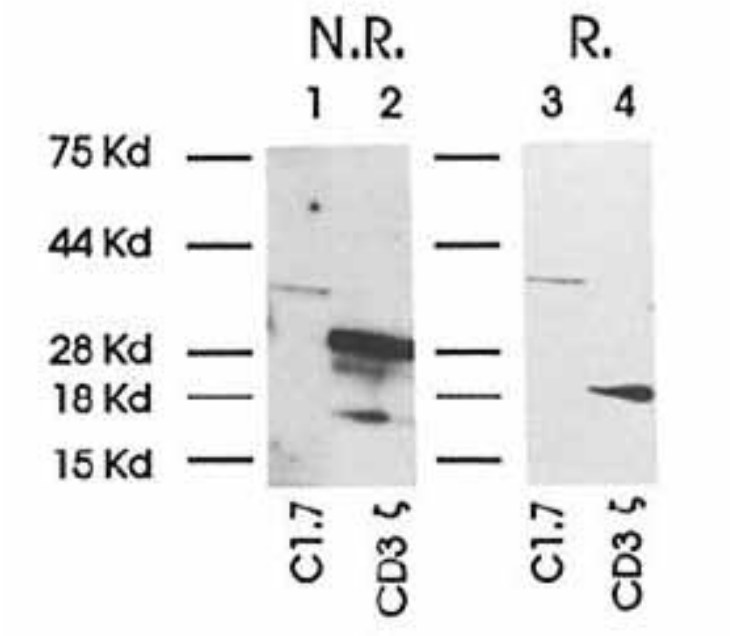
The third piece of prior art was U.S. Patent No. 5,688,690, to Valiante and Trinchieri (Valiante patent), as illustrated by the representative drawing reproduced in Figure 6, although the drawing actually appeared in the authors' publication (published within the one-year grace period) and was merely described in the Valiante patent.[15] This other prior discovery in the Valiante patent was related to a NKAR activating receptor in the human, called P38.

The immunoblot analysis shown in Figure 6 of human NK cells probed with a monoclonal antibody (mAb C1.7), which was generated against human NK cells and mediated cell killing, identified a NKAR having a molecular weight of 38 kD (lanes 1 and 3).[16] It is true that the NKAR protein was separated from nature as a band on a gel. The NKAR protein weighing 38 kD, called P38, turned out to be NAIL. But the NAIL gene was never cloned or sequenced. To repeat, and in contrast, the *Kubin* invention is related to the cloning and sequencing of the gene for NAIL.

Figure 6: The Kubin *Prior Art: Valiante and Trinchieri Paper (1993)*



© Valiante and Trinchieri, 1993. Originally published in The Journal of Experimental Medicine. *Refer to Note 15.*

Binding Legal Precedent for DNA Inventions: *In re Deuel*

To determine whether the invention is patentable over the prior art, a court needs to conduct a factual and legal analysis. Additionally, under the theory of consistency in the law, known as *stare decisis,* the court must also follow binding legal precedent. In other words, a case must be decided the same way when the legally relevant facts are the same or substantially similar. Here, the binding legal precedent was *In re Deuel*, decided previously by the Federal Circuit in 1995.[17]

In *In re Deuel,* the invention was related to cloned and sequenced DNA encoding the protein HBGF (heparin binding growth factor). HBGF is useful for stimulating cell division and, thus, wound healing. Figure 7 illustrates the amino acid sequence of HBGF.[18] The sequence for HBGF goes from 1 to 168 and reads as depicted in Figure 7.

Figure 7: The Deuel *Invention: DNA Encoding the Protein HBGF*

```
Met Gln Ala Gln Gln Tyr Gln Gln Gln Arg Arg Lys Phe Ala Ala   15
Ala Phe Leu Ala Phe Ile Phe Ile Leu Ala Ala Val Asp Thr Ala   30
Glu Ala Gly Lys Lys Glu Lys Pro Glu Lys Lys Val Lys Lys Ser   45
Asp Cys Gly Glu Trp Gln Trp Ser Val Cys Val Pro Thr Ser Gly   60
Asp Cys Gly Leu Gly Thr Arg Glu Gly Thr Arg Thr Gly Ala Glu   75
Cys Lys Gln Thr Met Lys Thr Gln Arg Cys Lys Ile Pro Cys Asn   90
Trp Lys Lys Gln Phe Gly Ala Glu Cys Lys Tyr Gln Phe Gln Ala  105
Trp Gly Glu Cys Asp Leu Asn Thr Ala Leu Lys Thr Arg Thr Gly  120
Ser Leu Lys Arg Ala Leu His Asn Ala Glu Cys Gln Lys Thr Val  135
Thr Ile Ser Lys Pro Cys Gly Lys Leu Thr Lys Pro Lys Pro Gln  150
Ala Glu Ser Lys Lys Lys Lys Lys Glu Gly Lys Lys Gln Glu Lys  165
Met Leu Asp                                                 168
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The first of two pieces of prior art in the *Deuel* case was *Molecular Cloning: A Laboratory Manual* by Maniatis, Fritsch, and Sambrook (1982).[19] This was the Maniatis laboratory manual previously noted, but in its first edition.

The second piece of prior art was European Patent Application No. 0 326 075, naming Bohlen and Gautschi-Sova as inventors (the Bohlen application), as illustrated by the representative drawing reproduced in Figure 8. This prior discovery in the Bohlen application was related to a HBGF in the cow, because the SDS-PAGE analysis shown in Figure 8 identified a bovine, or cow, HBGF having a molecular weight of 18 kD (lane 2).

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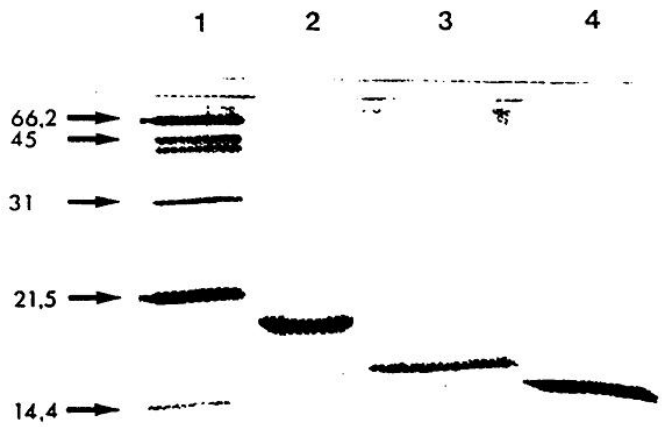
A human homologue of the bovine HBGF protein was also identified. A total of 19 amino acids were determined (amino acid 33 to 51 in Figure 7) for HBGF, which were found to be identical for human and bovine HBGFs. It is true that both the bovine and human HBGF protein had been separated from nature as a band on a gel. But neither the bovine nor human HBGF gene had been cloned or sequenced. To reiterate, and in contrast, the *Deuel* invention was related to the cloning and sequencing of the gene for HBGF.

Figure 8: The Deuel *Prior Art: Bohlen Application*



In re Deuel stands for the *old rule* that had guided the patenting of DNA for many years, specifically, that the existence of a general method of isolating DNA molecules is essentially irrelevant to the question of whether the specific molecules themselves would have been obvious and, thus, unpatentable. The Federal Circuit in *Deuel* reasoned that the applicant did not claim a method, but instead compositions. Accordingly, the issue was the obviousness of the claimed compositions, not the obviousness of the method by which those compositions were made. Therefore, a cookbook for cloning genes and a protein band found on a gel did not make the DNA sequence encoding the protein unpatentable (i.e., obvious).

In re Kubin: The Decision

Despite the legally relevant facts being essentially the same, the Federal Circuit did not decide *In re Kubin* the same way as *In re Deuel. Kubin* took the position that, in *KSR International Co. v. Teleflex Inc.,*[20] the United States Supreme Court had discredited

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the old rule of *Deuel*. While the Supreme Court did indeed seem to discredit one ruling of *Deuel* that "obvious to try" does not itself alone constitute obviousness, the Supreme Court did not discredit the other old rule of *Deuel* that the patentability of the sequence of the DNA molecule itself is unrelated to the method by which the gene is cloned. Nevertheless, the Federal Circuit panel in *Kubin* effectively overruled *Deuel*.

The Federal Circuit panel in *Kubin* concluded that the existence of a general method of isolating a DNA molecule is relevant to the question of whether the DNA molecule itself would have been obvious. So the obviousness of the method by which the gene is cloned could make the gene itself obvious. Continuing, the panel reasoned that it would have been "obvious to try" using the Maniatis laboratory manual. Additionally, there would have been a "reasonable expectation of success" in cloning the gene. This is because of an increased level of skill in the art (i.e., nucleic acid research) since *Deuel* was decided in 1995.

Therefore, a cookbook for cloning genes and a protein band found on a gel in the opinion of the Federal Circuit panel did indeed make the DNA sequence encoding the NAIL protein unpatentable (i.e., obvious). Because neither the United States Supreme Court nor the Federal Circuit itself (in an en banc decision of the entire court) reversesed this ruling by the *Kubin* panel, "the existence of a general method of isolating a DNA molecule is relevant to the question of whether the DNA molecule itself would have been obvious" will now be the new rule. In view of this panel decision, the question for many is whether the skill in the art in the laboratory has indeed progressed so far and what might be the implications for development and commercialization of inventions coming from basic research.

Commentary and Discussion for the Future

Try to imagine the amino acid sequence of NAIL, knowing that it is 365 amino acids long and that there are 20 amino acid choices at each position. The number of possibilities can be calculated mathematically. You have a 365 amino acid protein, and 20 choices for each amino acid, so there will be 20 to the power of 364 possibilities. Do not count the first amino acid because it is always Met. That is 20 times itself 364 times. This is a really big number, perhaps so big as to exceed the total number of particles in the universe!

In comparison to mouse NAIL, human NAIL turned out to show 54 percent amino acid identity, but which amino acids were identical was impossible to know until after the

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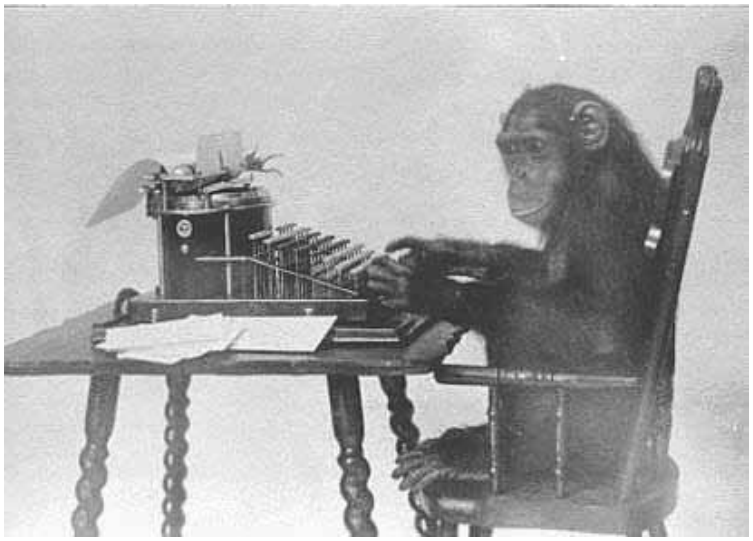
gene for NAIL was cloned. If you have an infinite number of monkeys sitting at an infinite number of typewriters for an infinite number of years typing at random then one would eventually type the entire works of Shakespeare (Figure 9). By analogy, given an infinite number of trials, you would eventually come up with the amino acid sequence of NAIL. Yet, creating an invention in the face of a nearly infinite number of possibilities is the first class of situations that the *Kubin* court agreed would *not* give rise to obviousness.

Figure 9: DNA Obviousness after Kubin*?*



Public domain photograph from Wikipedia

Emerson wrote: Build a better mousetrap, and the world will beat a path to your door. You cannot, however, patent an idea, e.g., the idea of building a better mousetrap. But you can patent a practical application of that idea, for instance, the actual prototype snap-trap mousetrap itself. Sure, "obviously" many scientists would have wanted to sequence the gene (a good idea), and the protocols for doing so apparently existed (Maniatis laboratory manual), but *Kubin* was first to actually sequence the gene. [21] And a form of invention, the result of exploring a general technology giving only generic guidelines and generalized instructions, is the second class of situations that the *Kubin* court agreed would *not* support obviousness.

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How do you reconcile the *Kubin* invention as falling into both of these two classes of situations that would *not* give rise to obviousness and as being ruled obvious? You scotch any precedent for the new rule. Is this new rule desirable when many economists believe that patents stimulate investment by fixing the "copying" problem so that a company can recover the cost of development, which for a new drug based upon a gene or other discovery to go from concept to FDA approval is cited to be on average $802 million?

Most all genes are cloned by the Maniatis laboratory manual. Most all chemical compounds are prepared by conventional chemistry processes.[22] Most everything in mechanical engineering (ME) and electrical engineering (EE) is a combination of well-known components. Under the reasoning of *Kubin*, gene sequence inventions, chemical compound inventions, and ME/EE inventions could arguably be unpatentable. Again, is this reasoning based on *Kubin* (taken to an extreme) desirable, even if it would contravene the patenting of most inventions?

With reference to the recent H1N1 flu virus, there is a need for a vaccine. Yet published reports indicate that "[v]accines against novel influenza A (H1N1) virus infection are being produced using methods similar to those used for seasonal influenza vaccines."[23] Extending the reasoning of *Kubin* to vaccines being produced using methods similar to those used in the art for making earlier vaccines, this vaccine could arguably be unpatentable in the United States. Once again, is this tentative result desirable given the need to attract investment in the development of technologies such as these arising from basic research?

The issue for research institutions is not only currently filed DNA sequence inventions being arguably unpatentable, but also certain DNA sequence patents being arguably invalid now.

Table 1: Comparison of Relevant Kubin and Deuel Dates

Name of Court Decision	Date of Court Decision	Date of Maniatis Prior Art	Filing Date of Patent Application
In re Kubin	3 Apr 2009	1989	Eff F/D = 23 Mar 1999
In re Deuel	28 Mar 1995	1982	21 Jun 1990

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Referring to Table 1, DNA sequence patents filed after the filing date of the patent application of *Deuel*, June 21, 1990, are susceptible to invalidation. This is because, under the reasoning of *Kubin*, DNA is arguably obvious since *Deuel*.

Tips for Technology Transfer Officers at Basic Research Institutions

Assuming that *In re Kubin* remains good law, a university technology transfer office (TTO) that has a new DNA sequence invention could describe how to make and use the invention without citing the Maniatis laboratory manual for the procedure on cloning the gene. The TTO would still submit the sequence data, and then go ahead and cite the Maniatis laboratory manual for the protocol on how to make the DNA *given* this sequence. But then you must be prepared to argue that cloning the gene could not have followed the Maniatis laboratory manual and optionally provide objective indicia of nonobviousness.

Objective indicia of nonobviousness mean considerations demonstrating that the subject matter sought to be patented is sufficiently different from what has come before so that it may be said to be inventive to that "hypothetical" person having ordinary skill in the art. Some such indicators include recognition by others, commercial success, and long-felt need. Another good argument for patentability is that the prior art teaches away from the claimed invention.

For NAIL, you could have argued that the Mathew article was published 1993, and the original Valiante and Trinchieri paper was published 1993, too. By contrast, the effective filing date of the *Kubin* patent application was 1999. That is six years after each of these references became public. If it was so obvious, why did it take six years to clone the NAIL gene? Additionally, you could have run the experiments to show that cloning the NAIL gene could not have followed the prior art, that using NK cells as a starting material failed, that using specially prepared NK cells activated by CD48 (or other nonobvious technique) was required to clone the NAIL gene. Finally, you could have argued unexpectedly superior properties of the NAIL gene.

The TTO might want to take a different approach by arguing that the *Kubin* lawyers lost based on a technicality. The argument goes that the prior art Valiante patent was unusually close to the *Kubin* invention, because the Valiante patent described the encoded protein band on a gel, prophetically applied the Maniatis laboratory manual to the problem

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of cloning the gene in Example 12, and made publicly available the very tool (mAb C1.7) for carrying out the method of cloning the gene. If the judges ruled narrowly in the *Kubin* case, then details that do not hew closely to the *Kubin* facts should save the research institution's DNA inventions from obviousness and unpatentability.

Although *Kubin* may have an adverse effect on the patenting of long-patentable genes, method-of-use patents should still be viable. Basic research institutions could offset *Kubin* by better identification of the function and use of the encoded proteins and focusing the patenting process on those properties and activities. Readers of *Kubin* may counter that the Federal Circuit seemed to find a biological feature that distinguished over the prior art (binding CD48) inherent to NAIL, thus not only was the product still obvious but also methods involving "inherent" biological features might also be unpatentable.

The rebuttal is that a method-of-use claim (e.g., administering NAIL to bind CD48), as opposed to a patent on a product, would be patentable, because a new and nonobvious use of even a known compound may be patentable over the prior art. Yes, method-of-use patents may be narrower than patents on the corresponding products. But the judiciary has apparently constrained the reach of Constitutionally authorized rewards for DNA sequence inventions.

Implications for Biotechnology Development

Under the central dogma of molecular biology, DNA sequence information has been everything. Under *Kubin*, DNA sequence inventions may arguably be unpatentable now. Perhaps the demise of the patenting of DNA inventions can be considered not a sea change but rather a reflection that molecular biology has evolved and advanced during past decades so that biotechnology itself has become more predictable. Various arguments (pro or con) from a scientific perspective can be made if indeed such "predictability" is now present or not, but it will be important to see if the U.S. Patent and Trademark Office and the courts extend such predictability to other requirements for patenting DNA inventions such as the "written description" and "enablement" of these inventions in a patent application.

Even with changing standards for patent protection, obtaining patents for DNA inventions remains a necessity for basic research institutions to attract private-sector firms to invest

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in these inventions to make new preventive, diagnostic, and therapeutic products. Thus by careful and prudent management of DNA inventions in their portfolio along the lines described above, these institutions should still be able to reach their goal of having new health-care treatments and services reach the public.

For more information on patents, see Volume 3 of the 3rd Edition of the Association of University Technology Managers Technology Transfer Practice Manual. *See also the chapter entitled "Understanding Patent Preparation and Prosecution," by Matthew S. Rudd, JD, and William E. McCracken, JD, in Volume 4.*

Notes

1. *In re Kubin,* 561 F.3d 1351 (Fed. Cir. 2009).
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3. U.S. Patent No. 6,284,491.
4. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).
5. *Hotchkiss v. Greenwood,* 52 U.S. 248 (1851).
6. Best Practices for the Licensing of Genomic Inventions, 70 Fed. Reg. 18413 (Apr. 11, 2005).
7. Pub. L. No. 96-517, now codified in 35 U.S.C. §§ 200-212. Regulations for implementing the Bayh-Dole Act are found at 37 C.F.R. §§ 401.1-401.17.
8. Pub. L. No. 99-502.
9. U.S. Patent Application No. 09/667,859.
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12. Joseph Sambrook, Edward F. Fritsch, and Thomas Maniatis, *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 2d ed. 1989).

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13. Porunelloor A. Mathew, Beth A. Garni-Wagner, Kevin Land, Akira Takashima, Earl Stoneman, Michael Bennett, and Vinay Kumar, "Cloning and characterization of the 2B4 gene encoding a molecule associated with non-MHC-restricted killing mediated by activated natural killer cells and T cells," *J Immunol.* 151 (1993): 5328-5337.
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16. Because NAIL was separated as a protein band on a gel, the protein was in the prior art.
17. *In re Deuel,* 51 F.3d 1552 (Fed. Cir. 1995).
18. U.S. Patent Application No. 07/542,232.
19. Thomas Maniatis, Edward F. Fritsch, and Joseph Sambrook, *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1982).
20. *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007).
21. PatentlyBIOtech, "The Blunders of *In Re Kubin,*" April 8, 2009, http://patentlybiotech.wordpress.com/2009/04/08/the-blunders-of-in-re-kubin/.
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