Non-obviousness in Patent Law: Impact of New Scientific Discoveries on In Re Kubin

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Non-Obviousness in Biotechnology Patent Law: Impact of new scientific findings on *In Re Kubin*

I. Introduction

The Federal Circuit made a recent controversial decision in *In Re Kubin* in applying the *KSR v. Teledex* obviousness criteria to the field of biotechnology.\(^1\) The *Kubin* decision was contrary to precedent, and overturned some prior cases while restructuring previously overturned cases into the rubric of *KSR*. As the legal world contemplated the implications of *KSR* on the field of biotechnology, a new scientific discovery was made which addresses the fundamental logic of an element of *Kubin*.\(^2\) The impact of the new scientific discovery on *In Re Kubin* suggests (a) *Kubin* should be limited to its facts, and (b) the scope of subject matter in the non-obvious “obvious to try” category should be significantly expanded, enabling greater patentability on new biotechnology inventions which incorporate this new scientific discovery.

As *Kubin* is relevant to the growing field of biotechnology, a brief explanation of the pertinent aspects of molecular biology will be presented. Next, the legal requirements of patentability will be presented to serve as a background for how obviousness is applied to the field of biotechnology. Then, a recent discovery on the non-degeneracy of the genetic code will be introduced. This is the key new scientific advance which calls into question one of the elements of *In Re Kubin*. Yet, this scientific

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\(^1\) *In Re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009)

advance was foretold is one aspect in the §112 Written Description requirements.
Finally, the impact of the particular scientific discovery on case law going forward will be discussed.

II. Scientific Background

The particulars of applying the obviousness tests in biotechnology involve an involved understanding of molecular biology. While this work is not intended to be a scientific publication, an introduction to molecular biology for the general audience reader will be presented. An additional introduction to molecular biology for the general audience attorney can be found in the In re O’Farrell case.

Molecular biology is the science of DNA. DNA is a shorthand descriptor for Deoxyribonucleic acid, a complex series of molecules linked together in a linear chain pattern. DNA is present in most of the cells of the human body. The same copy of DNA is present in all the various different cell types of the human body. But different parts of the DNA are being used by the cell depending on the cellular function. DNA consists of two long chains of nucleotides that wind around each other to form a double helix. Only four possible nucleotides (molecules) exist and are abbreviated with the simple letters: T, C, G, or A (the letters stand for a complicated molecular name that is beyond the scope of this work). Thus, a particular DNA sequence may be described in a series of letters, such as: ATCGCAATTTA. The two strands in the double helix are held together

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3 In re O’Farrell, 853 F.2d 894 (Fed.Cir. 1988)
4 Solomon, E.; Davis, P.; Villee, C.; "Biology". Saunders College Publishing, New York. 1985. (the entire section describing the biology of DNA in this work can be attributable to an educational text such as this reference)
with a weak form of chemical bond – a hydrogen bond. The nucleotide A will only
hydrogen bond with the T nucleotide (and vice versa). The nucleotide C will only
hydrogen bond with the G nucleotide. This results in two strands which are exact
opposites of each other. This results in a “double helix”, which is merely the same
sequence, but with one strand being the opposite of the other.

The mechanism by which a part of the DNA creates the protein is through a
process termed “translation”. First, DNA is converted into RNA (Ribonucleic Acid), which
is an intermediary molecule specific for the part of the DNA which needs to be read
depending on the cellular function. The RNA molecule is then converted into the
protein. The protein is a linear amino acid chain which folds up into a complex 3-
dimensional shape. It is the shape that actually determines the functional properties of
the protein. This simple explanation is only part of the story, as some RNAs are active on
their own, and do not carry forward into making proteins.\(^5\) This is the basis of the *In re
O’Farrell* case, which will be discussed below.

The cellular process of making proteins is complicated by the fact that the
nucleotides of the gene portion of DNA are rarely consecutive. Instead, they typically
consist of multiple coding portions, known as exons, separated by multiple non-coding
portions, known as introns. In humans and other species, when mRNAs are made, the
portion corresponding to introns must be excised or spliced of an intermediary form of
RNA to form the final mature form of RNA (mRNA). As a summary, the process flow of
how DNA is translated into proteins: genomic DNA → mRNA → protein. However, it’s
possible to go somewhat in reverse: cDNA ← mRNA, where mRNA can be “reverse

transcribed” to yield a form of DNA. The cDNA is termed “coding DNA” (as DNA is composed of both coding and non-coding regions, and the mRNA is just the transcribed coding regions of the genomic DNA).

The critical element of the protein translation process is that three specific DNA (and thus RNA) molecules, a “codon”, will create 1 specific amino acid each and every time. Thus, the same DNA sequence will always create the same amino acid sequence (and thus protein) each and every time it is read. The DNA sequence which translates into a specific protein is termed a “gene”. The mathematical possibilities of biological diversity starting from four nucleotides means there are 64 combinations ($4^3$) of sequences three nucleotides in length. Also, the order of the sequence is non-palindromic, in that “ATC” is NOT equivalent to “CTA”. There are only 20 amino acids in the human body. Thus, some amino acids are coded for by more than one codon, but each codon codes for at most one amino acid. This is the origin of the term “redundancy” or “degeneracy” of the genetic code. The degeneracy of the code gives has implications for claims for DNA and proteins. Once the nucleotide sequence of a DNA molecule has been determined, the amino acid sequence of the encoded protein can be easily ascertained. However, because of the code’s degeneracy, the reverse is not necessarily true. A protein having a known amino acid sequence (with over 1000 amino acid molecules) may be encoded by millions of possible codon combinations. An additional complication is that the linear amino acid sequence which makes up the protein is not entirely determinative as to the function of that protein. The linear amino acid sequence adopts a secondary structure, such as an alpha-helix or a beta-sheet, which then folds on itself to form a tertiary structure. As
Biology is a 3-d science, it is the 3-d structure of the protein which forms the functional element of the protein.

There are genes (and thus proteins) for various human diseases. For example, when the DNA for a particular protein changes, it is reflected in the replicated DNA of that same cell type which is newly created. The new cell type then has a mutated gene. Mutations in a DNA sequence can include missing DNA molecules, added DNA molecules, or changed DNA molecules. For example, the sequence ATGC could have the mutation ATC if the G were missing during the replication process. Also, the same sequence would be ATTC if the G were mutated into a T during the replication process. Because the codon of DNA includes three linear DNA molecules, the result of the above changes would be (for the first three DNA molecules) ATG would become ATC for the missing mutation, or ATG would become ATT for the change mutation. Because ATG, ATC, and ATT each code for different amino acids, the effect of a mutation in the DNA would be a change in the amino acid sequence of the protein formed. The effect of the change in the amino acid sequence of the protein formed would be on the ability of the protein to perform its cellular function.

III. Patentability in Biotechnology

As a brief roadmap, this work will discuss the impact of a new scientific discovery on the obviousness standards which the Federal Circuit has been applying to biotechnology claims. The obviousness standard is but one element which a claimed invention must meet to be patentable. As a general rule, to be patentable the claimed invention must satisfy the utility and subject matter requirements of 35 USC
§101, the novelty requirements of 35 USC §102, the written description and enablement requirements of 35 USC §112, and the non-obvious requirement of 35 USC 103. This work is focused on the non-obvious requirement of 35 USC §103.

Obvious is defined as being more than “better”, but actually “different”. In *Hotchkiss v. Greenwood*, the Court held that merely making something better did not imply that the invention was non-obvious, but only that the invention was of increased utility. The Court required differentiation from the prior art to be non-obvious. The measure of differentiation was based on the standard of an ordinary person having skill in the prior art (per the definition given in *Environmental Designs v. Unions Oil*) – that if they were able to make the differentiation, then the claimed invention would be obvious. In the realm of biotechnology, differentiation is measured by the function of the claimed invention, and not the specific nomenclature used to describe the invention. In *In re Papesch*, the Federal Circuit held that the similarity of a molecular formula in the prior art and in the claimed invention did not amount to obviousness, as the function of the molecules was distinctly different to indicate that the claimed invention was not obvious in light of the prior art. However, in *In re Dillon*, the en banc hearing of the Federal Circuit held that if prior art makes the compounds “obvious to try” for the new use based on the structure alone, then the claimed invention would be deemed to be obvious. In *Dillon*, the prior art disclosed a particular form of a

8 *Environmental Designs v. Unions Oil*, 713 F.2d 693, 696 (Fed. Cir. 1993).
9 *In Re Papesch*, 315 F.2d 381 (CCPA 1963).
10 Id.
11 *In re Dillon*, 919 F.2d 688 at 693, 696 (Fed. Cir. 1990) (en banc).
chemical molecule, with a specific use in the fuels additive field. The claimed invention was for a slightly different chemical molecule, and for a slightly different use in the fuels additive field. The court held that the new molecule was effectively suggested by the prior art molecule, as they were both applied to the same field. The restriction on patentability of new molecules regardless of prior art molecules indicates that the court focuses on a non-obvious differentiation of use. For example, in biotechnology a DNA molecule of a claimed invention which is close to that of another DNA in the prior art may be found to be non-obvious if the DNAs code for distinctly different proteins. However, if the DNAs code for the same protein, with no different features of the protein, then the claimed invention DNA would be found to be obvious.

The factors by which a claimed invention is screened for obviousness was established by the Court in *Graham v. John Deere*; (1) the scope and content of prior art; (2) the difference between the prior art and the claims in issue; (3) the level of ordinary skill in the pertinent art; and (4) which, if any, secondary considerations are relevant and their effect. Such secondary considerations are whether the claimed invention meets some unmet need, and whether others have failed at achieving this need. These elements are then evaluated to determine whether one having ordinary skill in the art would have made the invention. If one having ordinary skill in the art would have made the invention, the claimed invention is deemed to be obvious, and thus not patentable for failing to meet the requirement of 35 USC §103. In the *Graham* case, the claimed invention was for a plow, where a hinge point was changed from a

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12 Id.
14 Id.
similar plow in the prior art. The Court found the mere change in the hinge point to be something which a “simple mechanic” could employ, and thus obvious to one possessing knowledge in the art.\textsuperscript{16} In biotechnology claims, the application of the \textit{Graham} factors is applied to whether the invention as a whole (not merely the combination of two prior arts in a unique manner) was obvious to a person of ordinary skill in the pertinent art (e.g., genetics, immunology, biochemistry, etc.) at the time the invention was made.\textsuperscript{17} Thus, as the understanding of the field of science evolves, the court can not apply a retrospective analysis on the obviousness of the claimed invention with the new understanding of the science. So if a new discovery were made that made an issued patent now seem obvious, the court could not invalidate the patent for non-obviousness.

Prior to the \textit{KSR} case, the holding of \textit{In re Rouffet} applied for determining obviousness based on prior art.\textsuperscript{18} In \textit{In re Rouffet}, the Federal Circuit was concerned with the issue of a retrospective analysis being performed on prior art to make a claimed invention obvious. The Federal Circuit in \textit{Rouffet} held that there must be “teachings”, “suggestions”, “motivations”, or “disclosures” in the prior art (or trends in the industry) for one possessing ordinary skill in the art to make a claimed invention obvious. In the growing field of biotechnology, “motivation” may be the scientific interest in studying a gene which exists for a particular disease. Such a broad

\textsuperscript{16} See ref. 4
\textsuperscript{17} \textit{Hybritech v. Monoclonal Antibodies, Inc.,} 802 F.2d 1367 (Fed. Cir. 1986).
\textsuperscript{18} \textit{In Re Rouffet}, 149 F.3d 1350 (Fed. Cir. 1998).
application of the “motivation” test has some commenters concerned that no new

gene could be patentable, as the “motivation” for discovering it is already present.¹⁹

However, there is a recent line of case law which deals with an “obvious to try”

standard, particularly in the relatively unpredictable field of biotechnology. There are

four main cases which lead into In re Kubin in dealing with the “obvious to try” standard:

In Re Deuel, In Re Bell, In Re O’Farrell, and KSR v. Telex.²³ The cases waver on

whether to apply the “obvious to try” standard, then conclude in In Re Kubin which

ultimately allows the standard to apply, but with several exceptions.²⁴

In In Re Deuel, the court was presented with the issue of whether “obvious to try”

was an applicable standard for assessing the non-obviousness of a claimed DNA

sequence. In clarifying the “motivation” standard for obviousness, the court stated “a

general incentive does not make obvious a particular result, nor does the existence of

techniques by which those efforts can be carried out.”²⁵ However, a more specific

motivation may make obvious a prior art if the “prior art teachings suggest the claimed

compounds to one possessing ordinary skill in the art.”²⁶ The court was applying the

Rouffet “teach, suggest, or motivate” test with regards to the prior art.²⁷ In Deuel, the

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¹⁹Stephen R. Munzer; Commons, Anticommons, and Community in Biotechnology Assets, Theoretical Inquiries L. 271, At 284 (2009).

²⁰In Re Deuel, 51 F.3d 1552 (Fed.Cir. 1995)

²¹In Re Bell, 991 F.2d 781 (Fed. Cir. 1993)

²²In Re O’Farrell, 853 F.2d 894 (Fed. Cir. 1988)


²⁴See ref. 1

²⁵Deuel at 1559.

²⁶Deuel at 1557-8.

²⁷See ref. 15.
claimed invention was for a DNA sequence and the full amino acid sequence of the protein, but the prior art only disclosed a partial amino acid sequence to the protein. The inventors first isolated the protein, then determined the amino acid sequence of part of that protein (which was a different part of the protein amino acid sequence disclosed in the prior art). The inventors then they made a DNA probe based on the amino acid sequence (a process which was truly novel), and they used the DNA probe to scan a DNA library of a new type of tissue to identify the full DNA gene for the protein. The inventors subsequently determined (through standard laboratory procedures, which was cited as a second prior art) the DNA sequence of the gene. However, as the prior art was silent about DNA which was used to make the amino acids disclosed, then due to the degeneracy of the genetic code, it would have been impossible to pick out the claim invention’s 2 DNA sequences from among the 10^36 possible based on the known amino acid sequence in the prior art. Because the prior art potentially disclosed a genus of codon possibilities, and the claimed invention would have been but a species (subset) of the genus, the court applied the holding of In Re Baird, “a broad genus does not necessarily render obvious each compound within its scope”.28 From an amino acid sequence of a protein, there may be many possible DNA to encode for it, and thus if there is but 1 specific claim to a particular DNA sequence, it should not be found to be obvious from the existence of the 10^36 possible DNA sequences from the protein sequence. However, the Deuel court also noted that if the genus were particularly small and limited, then it would render obvious

28 Deuel at 1559 (citing In re Baird, 16 F.3d 380 (Fed.Cir. 1994))
each compound within its scope. But this exception is not applicable to highly complex species such as DNA and proteins.

The Deuel court held the claimed invention to be non-obvious over the prior art, as the court noted the novelty of ascertaining the DNA sequence despite the prior existence of a partial amino acid sequence: “knowledge of a protein does not give a conception of a particular DNA encoding it.” Furthermore, the court noted that even if it were “obvious to try” to discover the DNA sequence from the partial amino acid sequence, the “obvious to try” standard was not applicable, and thus the claims are non-obvious. This statement should be broken down into two components: (1) “even if it were”, and (2) the “obvious to try” standard was not applicable. Subsequent criticism of this case is based on the second part of the statement (as will be discussed below), but the recent discovery of a new paradigm in molecular biology (which will be discussed below) negates the hypothetical in the first part of the statement. Because knowing the specific DNA sequence is absolutely required to know the functional protein thus formed (as will be discussed below), merely knowing part of the amino acid sequence is not enough (nor is knowing the entire amino acid sequence), as there are many possible DNA codons which can encode for those amino acids. Thus discovery of the specific DNA sequence which codes for the functional protein would be non-obvious, regardless of whether the “obvious to try” standard were applicable. So the outcome of Deuel would remain the same, despite KSR’s later repudiation of Deuel’s block on the “obvious to try” standard.

29 Deuel at 1559 (citing In Re Petering, 301 F.2d 676 (CCPA 1962)).

30 Deuel at 1552.
The Federal Circuit further established the “teaching, suggestion, motivation” requirement of prior art to make obvious a claimed invention in biotechnology in the In Re Bell case.\textsuperscript{31} In Bell, the claimed invention was for several disclosed DNA sequences which encoded for variants of a particular protein (insulin).\textsuperscript{32} The prior art disclosed the amino acid sequences for these proteins. To begin with, the court notes the scientific incorrectness of the initial PTO decision which stated “it is clear from the (prior art) that the ordinary artisan knows how to find the nucleic acid when the amino acid sequence is known.”\textsuperscript{33} The court declared “the issue before us is whether the (PTO) correctly determined that the amino acid sequence of a protein in conjunction with a reference indicating a general method of cloning (a gene from a protein in isolated native 3-d form) renders the gene prima facie obvious.”\textsuperscript{34} The court applied the Deuel holding to these facts, and found that the prior art did not teach, suggest, or motivate one having ordinary skill in the art to make the claimed invention based on the existence of a full amino acid sequence. Applying a similar logic of In Re Deuel, the court noted that the mere existence of an amino acid sequence could be made with $10^{36}$ different nucleotide sequences, but the claimed invention is only for about 16 of them. However, the court noted that there may be an exception to this rule, such as in “a case in which a known amino acid sequence is specified exclusively by unique codons, the gene might have been obvious”.\textsuperscript{35} This could occur since there would be a unique 1:1 correlation between the amino acid and a codon (3 nucleotides). With the recent

\textsuperscript{31} See ref. 20

\textsuperscript{32} Id.

\textsuperscript{33} Id. at 783 (citing Ex Parte Bell, App. No. 2005-0866 (B.P.A.I.2004).

\textsuperscript{34} Id.

\textsuperscript{35} Id. at 784.
discovery of the non-degeneracy of the genetic code, a particular DNA sequence will always encode for a particular protein. Thus, disclosure of DNA should make obvious a claimed protein sequence. In summary, *In re Bell* held that the prior art must “teach, suggest, or motivate” to make the claimed invention obvious.\(^{36}\)

The Federal Circuit first hinted that an alternative obviousness test could be applied in *In re O’Farrell*.\(^{37}\) The claimed invention in *O’Farrell* was found to be obvious because the prior art contained detailed enabling methodology for practicing the claimed invention, and also a suggestion to practice the claimed invention, and also evidence that the method of practicing the claimed invention would work. Thus, the claimed invention was “obvious to try”.\(^{38}\) The court noted that “obvious to try” is not the standard (for obviousness) under § 103, nor is “obvious to try” the standard for non-obviousness under § 103.\(^{39}\) The court noted that there are two exceptions to the “obvious to try” category which would yield a non-obvious claimed invention, “It is true that ‘obvious to try’ is not the standard under §103. However, the meaning of this maxim is sometimes lost. Any invention that would in fact have been obvious under§ 103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless non-obvious?”\(^{40}\) The two exceptions were (a) when there is the situation where “to try each of a numerous possible choices until one possibly arrived at a successful result, where the prior art either gave no indication of which parameters were critical of no direction as to which of many possible choices

\(^{36}\) *Id.*

\(^{37}\) See ref. 21

\(^{38}\) *Id.*

\(^{39}\) *Id.*

\(^{40}\) *Id.* at 903.
is likely to be successful," and (b) when the situation is "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.” 41 Both exceptions share the common characteristic of “a
possibility of unexpected results”, which is the basis for the practical non-obviousness.42
With the uniqueness of DNA, choosing from among millions of potential DNA codon
sequences for a particular amino acid sequence would be equivalent to the first
exception outlined in O’Farrell, thus a claimed invention of DNA in light of the disclosure
of amino acid sequences would qualify as an exception to the general “obvious” rule.

In 2007, the Supreme Court addressed the issue of obviousness with respect to the
mechanical arts in KSR v. Teleflex.43 While the facts of KSR concern a mechanical
design for a device, the holding of KSR has been extended to the biotechnology field in
Kubin “This court also declines to cabin KSR to the ‘predictable arts’, as opposed to the
‘unpredictable art’ of biotechnology”.44 The court followed that little quote with a
recitation from In Re Papesch, “the problem of ‘obviousness’ under S.103...is not really a
problem in chemistry or...any other related field of science. It is a problem of patent
law”.45 Thus, KSR holds for patents in the field of biotechnology. The holding of KSR has
been extensively analyzed in various law review articles, and so this work would merely
be superfluous in light of recent articles on the matter in attempting to describe the

41 O’Farrell at 903.
42 Id.
43 See ref. 22
44 Kubin at 1360.
45 Kubin at 1361 (citing In Re Papesch, 315 F.2d 381, 386 (CCPA 1963)).
Kubin case. Nonetheless, a brief explanation of the impact of KSR on biotechnology is in order to establish a background for In Re Kubin.

The Supreme Court in KSR altered the interaction of the applicable tests for obviousness, the factors given in Graham, and the teaching-suggestion-motivation test. The Court referred to the “teaching-suggestion-motivation” test as merely “helpful insight” into the Graham factors, and was not an absolute rule. In KSR, the claimed invention was combined an electronic sensor with an adjustable car pedal, which allowed the car’s internal computer to transmit information regarding the position of the pedal to the throttle. There were various prior art references disclosing electronic sensors, placement of pivot points in adjustable care pedals, and even placing electronic sensors on part of a pedal (but which resulted in a non-optimal product performance). The district court found that the claimed invention was taught or suggested by the prior art, and was thus obvious. The Federal Circuit thought otherwise, as the prior art was targeted at a different purpose. The Supreme Court granted certiori and held that the teaching-suggestion-motivation test applied by the Federal Circuit from In Re Rouffet was too strict of a test for obviousness. Furthermore, the Court expanded the ability of a person of ordinary skill in the art to have a

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47 See ref. 12
48 KSR, 127 S. Ct. at 1739-43.
49 Id. at 1741.
50 KSR at 1734.
51 Id.
53 Teleflex, 119 F. App’x at 288-89.
54 KSR, 127 S. Ct. at 1739.
motivation for doing the claimed invention based on the prior art by enabling the hypothetical person of ordinary skill in the art a level of common sense and creativity.\textsuperscript{55} The Court also rejuvenated the “obvious to try” standard:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, 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, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.\textsuperscript{56}

The net impact of KSR is that a greater scope of prior art can now be used to deem a claimed invention obvious.

In April 2009, the Federal Circuit delivered the \textit{In Re Kubin} decision, which applied the “non-test” for obviousness from \textit{KSR} to biotechnology claims.\textsuperscript{57} Prior to discussing the legal analysis of \textit{Kubin}, a brief recitation of the facts of \textit{Kubin} will be presented to establish a background for the impact of a new scientific discovery on \textit{Kubin}. The claimed invention of \textit{Kubin} was for the process of isolating, and the human DNA sequence encoding for, a protein which is found on cell surfaces and is important in fighting tumors. The protein (“NAIL” – Natural Killer Cell Activation Inducing Ligand). In particular, claim 73 covered “an isolated nucleic acid, which codes for a protein which can bind to CD48.”\textsuperscript{58} Effectively, this claim is attempting to claim all DNAs which

\textsuperscript{55} Id. at 1742.
\textsuperscript{56} Id.
\textsuperscript{57} See ref. 1
\textsuperscript{58} \textit{Kubin} at 1353.
code for this a protein with this particular property. The specification describes the cDNA sequence of the NAIL protein (the DNA sequence which only codes for the protein), and the sequence of DNA with the intronic regions (the DNA sequence which codes for the protein linked to junk DNA which is spliced out during the transcription process).59

(The PTO rejected the claimed invention in Kubin per §112 and per §103. However, the Federal Circuit only took up the §103 obvious issue, and found that since the patent was invalid for being obvious, it did not address the §112 issue.60)

The facts and legal issues of Kubin and Deuel are similar (Deuel was decided in 1995 and Kubin in 2009). Both cases involved a claimed DNA molecule encoding a known protein. The claimed inventions in both Kubin and Deuel were rejected as being obvious under § 103 in view of prior art that disclosed the amino acid sequence of a known protein and a general method of isolating or cloning DNA molecules. None of the prior art references cited in Kubin nor Deuel suggested the specific DNA sequences of the claimed inventions. The Federal Circuit in Deuel found the claimed DNA molecules to be nonobvious because “the prior art does not disclose any relevant (DNA sequences of) molecules...”61 The Federal Circuit applied the classic ‘difference’ test of Hotchkiss v. Greenwald to ascertain obviousness.62 As the facts and legal issues of Kubin and Deuel are similar, Deuel should have applied to the Kubin case. However,

59 Id.
60 In re Kubin, at 1351.
61 In re Deuel at 1558.
62 See ref. 7
the PTO in *Kubin* disagreed with the appellants, and distinguished the case from *Deuel* based on the increased level of skill in the art and other “factual differences”.

In *Kubin*, the prior art disclosed the exact same protein, termed “p38”, as that in the claimed invention, but it did not disclose the specific amino acid sequence nor the DNA sequence which encoded for it. Prior art also suggested that the DNA sequence could be obtained with the use of a standard laboratory manual (the same manual which the inventors actually used). The Federal Circuit noted that since the claimed invention merely utilized a common lab procedure for isolating their protein, that this process was not patentable. The only element of the claimed invention remaining was the composition of matter claim, that of the DNA sequence. Next, the Federal Circuit applied the only distinction of NAIL protein in the claimed invention over that of the prior art. The court held that the ability of the NAIL protein to bind to another type of protein, CD48, was merely a feature of the protein which was also present in the prior art, but just not ever detected by the prior art, “It is not invention to perceive that the product which others had discovered had qualities they failed to detect”. Thus, a claimed invention will not be non-obvious merely because of the discovery of a new feature on a prior art material.

Because the PTO reincarnated the “obvious to try” method for obviousness in analyzing the claimed invention in *Kubin*, the Federal Circuit was presented with an

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64 *Id.* at 1354.

65 *Id*.

66 *Kubin* at 1356.

67 *In Re Kubin* at 1357 (citing *GE v. Jewel Incandescent Lamp*, 326 US 242, 249 (1945)).
opportunity to interrelate *In Re Deuel* in light of *KSR* in reviewing the PTO decision.68 *Kubin* noted that in *KSR*, the “Supreme Court repudiated as error the *Deuel* restriction on the ability of a skilled artisan to combine elements within the scope of the prior art...When there is a design need, obvious to try might show that it was obvious under §103.”69 With the “might” qualifier, this suggests that “obvious to try” is a subset of “obvious under §103. The *Kubin* court noted as such from *In re O’Farrell* as “obvious to try” is a broader classification that “obvious”, and recited the two exceptions listed in *O’Farrell* from “obvious to try” which are non-obvious.70 The *Kubin* court then noted that when the prior art provides a means and a suggestion for practicing the claimed invention, and that the two *O’Farrell* exceptions did not apply (as there was a reasonable expectation of success in practicing the claimed invention based on the prior art), then the claimed invention is void for lack of non-obviousness. Thus, the prior art teaching the existence of the p38/NAIL protein, and also teaching specific enabling help for obtaining the DNA sequence, will invalidate the claimed invention. Another facet of the *Kubin* holding is that because the isolation of the p38/NAIL protein was motivated merely because of its importance to human health (based on the prior art), then it a sufficient motivation exists to make obvious its isolation.71 Several commenters have discussed the impact of this second holding on the patentability of gene sequences.72,73 However, others have noted that because this part of the holding was

69 *In Re Kubin* at 1359 (citing *KSR v. Telefex* at 421)
70 *Id.* (citing *O’Farrell* at 903)
71 *Kubin* at 1360.
limited to the isolation process, and not the product claim for a new DNA sequence, so that the patentability of DNA sequences remains intact.74

A set-subset chart of the various types of obviousness under the “obvious to try” rubric is shown below in Figure 1. The only subset of “obvious to try” claimed inventions which will be deemed obvious, and thus not patentable under §103 will be those that do not meet the exceptions for non-obviousness. The first exception from “obvious to try” which is non-obvious, such as where there are a trillion possibilities and the prior art provides no guidance in narrowing down the candidates to try, is applicable to the case of amino acid sequences which may not make obvious their genes (the “possibility” is a numbers game). The second exception, where prior art merely gives general guidance to pursuing a new technology, is applicable when a claimed invention is specific in a new technology field, but the prior art is general and non-guiding. In biotechnology claims, the second exception may apply when the non-degeneracy of the genetic code (which will be discussed below) suggests that any amino acid sequence can not (in an absolute sense) make obvious the encoding gene. Thus, the impact of the recent discovery of the non-degeneracy of the genetic code is to strictly apply the rule that “mere existence of a protein sequence will not make obvious the gene encoding for it”.

IV. Recent scientific discovery of the non-degeneracy of the genetic code

This work would merely be superfluous with that of existing law review articles discussing the implications of KSR on biotechnology patents\(^\text{75}\) and the In re Kubin case\(^\text{76}\) if it did not add an additional element: newly discovered science. In 2007, researchers discovered that creating an artificial gene with substituted codons which should have encoded for the same amino acid in the resultant protein yielded a protein with a different 3-d shape.\(^\text{77}\) This mutant protein possessed different chemical functionality. The researchers hypothesized that “the presence of a rare codon, marked by the synonymous polymorphism, affects the timing of cotranslational folding and insertion of

\(^{75}\) See ref. 46.


\(^{77}\) See ref. 46.
(the protein) into the membrane, thereby altering the structure of substrate and inhibitor interaction sites (the chemical functionality of the protein).” In other words, the researchers explained that a single base modification (SNP – single nucleotide polymorphism) in a codon which yielded the same amino acid (thus, synonymous codons) produced a protein with a different chemical function. When DNA codon substrates are transcribed into mRNA, the mRNA is the actual chemical entity which is translated into proteins. As a protein is forming, it is still attached to the mRNA. Because different codons have different translation rates (that is, they pass through the enzyme which is associating each amino acid sequence to each codon at different rates), the movement of the protein outside of the cell nucleus is “stuttered” by the translation rate. This was known as early as 1995, but the effects of the stuttering on the protein’s 3’d shape were not known until the 2007 Science article. Because of the “stuttering”, the protein folds into a different 3-d shape. Also, it is known that the 3-d structure of a protein affects its chemical functionality, and so the rates of “stutter” will affect the functionality of the protein. The codon switch thereby will have an effect on the chemical functionality of the protein. Thus, the exact DNA sequence of a protein will affect the chemical functionality of a protein. The authors of the 2007 Science article were also able to measure the functional response of the mutated protein P-gp (P-glycoprotein) made from a mutated codon sequence versus the natural form of the protein.

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78 See ref. 4.


80 See ref. 4.
protein, and found the mutated protein to be much less active on the protein’s substrates.\textsuperscript{81}

The impact of this new scientific discovery in the area of non-obviousness of patent law is that the requirement to claim protein sequences will be much more strict. When making claims on proteins which perform a certain function, one is implying that the utility of the protein (§101 requirement) is met by the function which the protein performs. Thus, a protein claim should only be allowed if it is being made by the exact DNA sequence which codes for that 3-d structure. Instead of the possibility of a single protein which “might be” encoded by a specific set of codons, the paradigm is now that a single protein “must be” encoded by a specific set of codons. Since silent codon switches can now result in proteins with an identical linear amino acid sequence, an “inverse Papesch” test should be applied, where the manner in which a compound is written down (in this case, the linear amino acid sequence) is not enough to claim a particular protein, but rather the full DNA sequence needs to be disclosed.\textsuperscript{82}

The impact of the new scientific discovery on the subset of allowable “obvious to try” categories which are not §103 obvious is to expand the scope of one of the categories. From Figure 1, the category “A specific pursuit in a new technology, when prior art only gave general help” would be expanded with the new scientific discovery on the non-degeneracy of the functional genetic code as prior art protein sequences become limited in their predictability of DNA sequences and homologous protein sequences. As only functional proteins should be patentable under the §101 utility requirements, merely reciting the linear amino acid sequence of a protein to claim its

\textsuperscript{81} Id.

\textsuperscript{82} See ref. 8.
function would be insufficient. So prior art describing a protein in such a manner without a concomitant description of either its 3-d structure or the DNA sequence which was used to create that protein would amount to mere “general help” against an alternative DNA sequence which codes for that protein. Thus, this prior art would not make a claimed invention for an alternative DNA sequence §103 obvious, and so the claimed invention would be patentable. In the absence of the recent discovery of the non-degeneracy of the genetic code, the existence of a linear amino acid sequence, and a particular DNA sequence used to create that amino acid sequence, would make obvious any alternative DNA sequences (such as those in a possible claimed invention) which could also code for that protein. The effect is to increase the scope of what would be allowable under §103.

V. The non-degeneracy of the genetic code under §112 Written Description Requirement

The discovery that DNA is non-degenerate is more properly addressed with the 35 USC § 112 written description requirement. While this work is not intended to investigate the ramifications of the non-degeneracy of the genetic code on all aspects of patent law, a comparison with the § 112 requirements as established by case law will suggest a more proper approach to patenting within a scientific field which is subject to new paradigm changes. Furthermore, as Kubin was initially rejected by the PTO under both §112 and §103, and the Federal Circuit affirmed the §103 decision only (but passed on the §112 decision in light of the §103 rejection), if Kubin was not found to be

83 35 USC §112.
rejected under §103, then it functionally could still have the same result if it were rejected under §112.\(^84\) Indeed, the inventor-appellants argued in their reply brief that their claimed invention satisfied the §112 requirement per *In Re Wallach* (that the individual support for each species that the genus embraces is not required).\(^85\) However, the court denied the patent under §103, and so this section will only be focused on examining how the new scientific discovery of the non-degeneracy of the genetic code would have on patentability of DNA in general, and not specifically in *Kubin*.

Because the purpose of a patent is an agreement between the inventor with the general public for a temporary monopoly on creating, using, and selling that invention, after which the public can create and use the patent at the expiration of the patent term, the inventor owes the public the best written description of the invention possible. If the claimed invention is not adequately described, the public is not receiving its benefit of the bargain. Thus, the principle of ensuring the fairness of the bargain is the driver of the §112 written description requirement.

The Federal Circuit in *UC v. Eli Lilly* denied patentability of a class of DNA based on the §112 written description requirement because the claimed invention was not specific enough to allow one possessing ordinary skill in the art to reproduce the DNA.\(^86\) The claimed invention was for “mammalian DNA” for the insulin protein, but the patent specification only described “rat DNA” for the insulin protein. As rats are a subset of mammals, and the DNA sequence is not necessarily the same in all mammals, then the “rat DNA” sequence in the specification is not descript enough to enable one to create

\(^{84}\) See ref. 1.


\(^{86}\) *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997)
human insulin. The court declared that by describing a possible DNA sequence did not enable one to create the actual DNA, and so the actual DNA sequence must be described. In the court’s words “‘an adequate written description of a DNA . . . requires a precise definition, such as by structure, formula, chemical name, or physical properties,’ not a mere wish or plan for obtaining the claimed chemical invention.” 87 Because the specification did not provide the "relevant structural or physical characteristics" of the human gene, i.e., its genetic sequence, it did not provide adequate written description, regardless of whether the specification enabled the human gene. 88 The court also required more than a generic nomenclature for claiming DNA, as "vertebrate insulin (gene)," was insufficient absent a structural description that would enable one to distinguish genetic sequences falling within the scope of the claimed invention from other (prior art) non-claimed genetic sequences. 89 The court perceived the claimed genus of genetic sequences as being defined solely in terms of function, i.e., the ability to encode for insulin, and held that such a purely functional description was insufficient with respect to chemical inventions in general, and DNA sequences in particular. 90 A recent law review summarized UC v. Eli Lilly as “requiring a nucleotide-by-nucleotide recitation of the structure of a biotechnological invention.” 91 The claimed invention in Eli Lilly did not list a polynucleotide sequence. Thus, the claimed invention in Eli Lilly failed for lack of enablement and written description.

87 Lilly, 119 F.3d at 1566 (citing Fiers v. Revel, 984 F.2d 1164, 1171 (Fed.Cir.1993)).
88 Id. at 1567.
89 Id. at 1568.
90 Id.
91 Christopher Holman, Is Lilly Written Description a Paper Tiger?: A comprehensive assessment of the impact of Eli Lilly and Its Progeny in the Courts and PTO, 17 Alb. L.J. Sci. & Tech. 1 at 19 (citing Univ. of Rochester v. G.D. Searle & Co., 375 F.3d at 1308)
The PTO adopted a similar test prior to *Eli Lilly* in a case with facts similar to that of *Kubin* in *Ex parte Maizel*. In *Maizel*, the specification disclosed the amino acid sequence of a protein but the claimed invention was for any DNA vector (cDNA) encoding that protein or a "biologically functional equivalent thereof." The PTO held the claim invalid for lack of enablement, stating that the "problem with the phrase 'biologically functional equivalent thereof' is too broad, as it applies to any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor." Thus, prior to the *Eli Lilly* case the PTO applied a strict test which could be met with the disclosure of a linear DNA sequence.

However, the specific DNA sequence does not need to be described if there are alternative methods for enabling one possessing ordinary skill in the art to reproduce the claimed invention. In *Enzo Biochem, Inc. v. Gen-Probe Inc.* (*Enzo II*), the Federal Circuit held that depositing the DNA sequence in public directory is sufficient to enable others to reproduce the patent, even if the DNA sequence was not listed in the patent specification.

There is one “exception” to the strict requirement that the written description requirement can be fulfilled only by listing the entire DNA sequence. In *Invitrogen v. Clontech*, the Federal Circuit held that when the patent specification disclosed one protein which was made from the result of genetic engineering of the sequence of a known protein, then any variant of the known protein (made by the same genetic engineering process) would meet the §112 written description requirement because

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94 *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002).
the claimed invention covered any engineered variant of the protein sharing the modified function.\textsuperscript{95} Thus, because the DNA of the protein was known, and the process of changing the DNA was known (which resulted in some part of the DNA never changing when creating the variants, and this part of the DNA was responsible for the functional character of the protein), then by changing the DNA of this protein via this process could result in many variant proteins. All of the proteins were held to be patentable under §112, as the specification enabled one possessing ordinary skill in the art to reproduce the protein variants. When applying the recent discovery of the non-degeneracy of the genetic code to this “exception”, the holding should still stand, as the genetic code of the variants did not change, and thus the RNA translation rate would not change, and so the 3-d protein structure (of the functional component of the protein) would not change. Thus, the original \textit{Invitrogen} holding would be unaffected with the recent discovery of the non-degeneracy of the genetic code.

VI. Conclusion

A valid counterargument against globalizing the recent discovery of the non-degeneracy of the genetic code to all DNA sequences is that this is but one gene, and may not necessarily occur in other genes, akin to the legal adage “the exception does not prove the rule”. However, the researchers note that codon degeneracy occurs with different frequency in different species. Furthermore, as only two years have passed since this discovery, many other examples may exist but are yet to be discovered. So the prevalence of this new discovery on DNA degeneracy should be held as a possibility under a legal analysis. Because of the existence of a “possibility”,

\textsuperscript{95} \textit{Invitrogen v. Clontech}, 429 F.3d 1052 (Fed. Cir. 2005).
legal analyses of DNA claims under *In Re Kubin* should be construed under a new scientific paradigm – that not all DNA sequences which could code for a protein will create the same functional protein.

As the purpose of the judicial legal system is to “discover the law, not to create it”\(^6\), creating legal rules for new technologies runs the risk that the discovery process is not yet complete. In the field of biotechnology, new scientific discoveries are continuing to be made. The recent discovery of the non-degeneracy of the genetic code suggests that any law or holding which relied on the absolute degeneracy of the genetic code should be revisited. As *In Re Kubin* held that the prior existence of a protein sequence made obvious a claimed invention for a protein sequence concomitant with a DNA sequence\(^7\), then *In Re Kubin* should be held to the particular facts of the case. This part of the *Kubin* case is essentially wrong in light of the recent scientific discovery of the non-degeneracy of the genetic code. However, as another element of *Kubin* also relied on the obviousness of the method by which the claimed invention ascertained the genetic sequence from the claimed protein sequence, this aspect of *Kubin* could remain true and serve to justify the *Kubin* decision.\(^8\) Thus, the reach of *Kubin* should be limited to the specific facts presented, and the holdings of *In Re Deuel* and *In Re Bell* should continue to carry forth in biotechnology patents.


\(^{7}\) See ref. 1

\(^{8}\) Id.