A NAIL IN THE COFFIN FOR GENE PATENTS

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In 2007, the Supreme Court in *KSR International Co. v. Teleflex Inc.*[1] substantively addressed the obviousness standard for the first time since *Graham v. John Deere Co.*, which was decided over forty years ago.[2] In a unanimous opinion, the Court rejected the Federal Circuit's rigid employment of the teaching, suggestion, or motivation ("TSM") test, which had narrowed the scope of the obviousness inquiry.[3] Instead, the Court favored a flexible approach to the obviousness question and held that the obviousness inquiry should encompass a broader scope of prior art with allowances for common sense and creative inferences.[4] Furthermore, the Court appeared to ease the obviousness standard by stating that an invention might be obvious if it would have been "obvious to try" to a person of ordinary skill in the art.[5]

Federal Circuit precedent in the 1990s foreclosed use of the obvious to try test to invalidate gene sequence claims.[6] In *In re Deuel*, the Federal Circuit explicitly rejected obvious to try as the obviousness standard for gene patents.[7] The court held that the existence of general methods for isolating genes was "essentially irrelevant" for determining their obviousness in the absence of prior art suggesting the actual sequences.[8]

In *In re Kubin*, the Federal Circuit revisited the obvious to try test as applied to gene sequences under the post-*KSR* obviousness standard.[9] The court relied on *KSR* and one of its own decisions—*In re O'Farrell*, which predated *KSR*—to reject as obvious claims directed to the isolation and sequencing of a human gene encoding the protein Natural Killer Cell Activation Inducing Ligand (NAIL).[10] The court found that a prior art

1. 550 U.S. 398 (2007).
2. 383 U.S. 1 (1966).
3. *KSR*, 550 U.S. at 418–22.
4. *Id.* at 418, 421.
5. *Id.* at 421.
6. In re Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995) ("'Obvious to try' has long been held not to constitute obviousness."); *see* In re Bell, 991 F.2d 781, 785 (Fed. Cir. 1993) (holding that focusing on the methods of making the claimed sequences is misplaced).
7. 51 F.3d at 1559.
8. *Id.*
9. 561 F.3d 1351, 1352 (Fed. Cir. 2009).
10. *Id.* at 1361.

reference disclosing the existence of the NAIL protein, a prophetic method for isolating the gene encoding NAIL, and a probe for performing that isolation, along with a manual disclosing general methods for isolating a gene, rendered the cloning of the gene "reasonably expected in light of the prior art and 'obvious to try.'"[11] The court further interpreted *KSR* as overruling *Deuel* and held that the obvious to try test can apply to the "unpredictable art" of biotechnology.[12]

Part I of this Note introduces the law of obviousness, focusing on the development of the obvious to try test and key Federal Circuit decisions rejecting that approach for gene patents. It also includes a biotechnology primer describing the relationship between gene and protein sequences, and scientific methods for gene cloning. Part II describes the *Kubin* decision. Part III discusses *Kubin*'s probable implications and concludes that the decision represents a major change in the law that will lower the bar for finding biotechnology patents obvious.

I. BACKGROUND ON THE LAW OF OBVIOUSNESS

A. OBVIOUSNESS AND THE *GRAHAM* FRAMEWORK

The U.S. patent system aims to promote the progress of science and technology.[13] A patentable invention must be new, useful, and nonobvious.[14] The nonobviousness requirement codified in § 103 bars the grant of a patent if "the differences between the [invention] and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[15]

In *Graham*, the Supreme Court articulated a framework to evaluate obviousness.[16] That framework considers several factual inquiries, including the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art.[17] In this analysis, courts may also evaluate secondary considerations, e.g., commercial success, long felt but unsolved needs, and the failure of others to solve the problem.[18]

11. *Id.*
12. *Id.* at 1358, 1360.
13. *See* U.S. CONST. art. I, § 8, cl. 8.
14. 35 U.S.C. §§ 101–103 (2006).
15. 35 U.S.C. § 103(a) (2006).
16. Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966).
17. *Id.*
18. *Id.*

To fulfill the nonobviousness requirement, an invention must evidence more ingenuity and skill than that "possessed by an ordinary mechanic acquainted with the business."[19] *Graham* dealt with an invention that combined known mechanical elements in a different arrangement to create an improved device for absorbing shock from plow shanks.[20] The Court held that the invention was unpatentable because the differences between the claims and the prior art would have been obvious to a person reasonably skilled in the art at the time of the invention.[21]

The invention, however, need not evince a "flash of creative genius," a standard promulgated by the Supreme Court in *Cuno Engineering Corp. v. Automatic Devices Corp.*[22] The Court found that Congress had abolished the *Cuno* standard by adding "[p]atentability shall not be negatived by the manner in which the invention was made" to § 103.[23]

The Court also recognized the importance of the nonobviousness requirement in ensuring that the patent system awards patents for "innovation, advancement, and things which add to the sum of useful knowledge."[24] In contrast, an invention that merely adds trivial or incremental modifications to the prior art essentially exists in the public domain and fails to satisfy the nonobviousness requirement.

B. *KSR* AFFIRMS THE *GRAHAM* FRAMEWORK FOR EVALUATING OBVIOUSNESS

In the years following *Graham*, the Court of Customs and Patent Appeals (CCPA) and the Federal Circuit[25] developed and employed the TSM test to evaluate the obviousness of an invention.[26] Obviousness requires the factfinder to step back in time to evaluate the state of the art at the time of invention. Hindsight bias complicates these judgments. Awareness of the invention can distort the challenges facing inventors at the time of discovery, and a revolutionary invention may seem obvious with the passage of time. The TSM test carefully guarded against hindsight bias by requiring that the prior art, the nature of the problem, or the knowledge of a person of

19. *Id.* at 11 (citing Hotchkiss v. Greenwood, 52 U.S. 248, 267 (1850)).
20. *Id.* at 19–20.
21. *Id.* at 25–26.
22. *Id.* at 15 (citing Cuno Eng'g Corp. v. Automatic Devices Corp., 314 U.S. 84 (1941)).
23. *Id.*; 35 U.S.C. § 103(a) (2006).
24. *See Graham*, 383 U.S. at 6, 14.
25. In 1982, the CCPA and the US Court of Claims were combined to form the Federal Circuit.
26. *See, e.g.*, KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418–19 (2007).

ordinary skill in the art provide some motivation or suggestion to combine prior art teachings.[27]

In *KSR*, the Supreme Court criticized rigid application of the TSM test.[28] The case concerned a mechanical combination of an adjustable automobile gas pedal and an electronic sensor.[29] Although the prior art disclosed both elements,[30] the Federal Circuit refused to invalidate the patent because the prior art did not provide explicit motivation for a person of skill in the art to combine those elements.[31] The Supreme Court reversed and found that rigid reliance on the TSM test deviated from the flexible *Graham* framework.[32] The Court explained that the prior art encompassed more than references to the problem the patentee was trying to solve or elements designed to solve it.[33] Under the correct analysis, the prior art can consider "any need or problem known in the field or endeavor"[34] and include elements that a person of ordinary skill or creativity could fit together like "pieces of a puzzle."[35] Although the Court acknowledged that the use of hindsight remained a risk, the rigid TSM test overestimated its threat and denied "factfinders recourse to common sense."[36]

The Court further expanded the types of evidence that a court may consider by revitalizing the obvious to try test—previously rejected by the Federal Circuit.[37] According to the Court, the Federal Circuit incorrectly concluded that "a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'"[38] The Court elaborated that what is obvious to try might be obvious when "there is a design need or market pressure to solve a problem," "a finite number of identified, predictable solutions" exists, and pursuit of known options leads to "anticipated success."[39]

KSR generated uncertainty concerning the way in which lower courts would interpret and apply the expanded obviousness standard. In particular,

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27. *See id.* at 407 (quoting Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1323–24 (Fed. Cir. 1999)).
28. *Id.* at 415.
29. *Id.* at 410.
30. *Id.* at 407–09.
31. *Id.* at 414.
32. *See id.* at 415.
33. *Id.* at 420.
34. *Id.*
35. *Id.* at 420–21.
36. *Id.* at 421.
37. *Id.*
38. *Id.*
39. *Id.*

revitalizing the obvious to try test could dictate the viability of biotechnology patents going forward.

C. THE OBVIOUS TO TRY TEST

The concept of obvious to try originated in CCPA decisions preceding codification of the nonobviousness requirement in the 1952 Patent Act.[40] For example, in *In re Leum*, the CCPA employed the test to invalidate methods of producing toluene under superatmospheric pressure in closed chambers.[41] The prior art disclosed similar starting materials and overlapping temperature ranges but not closed systems.[42] The CCPA rejected the claims as obvious because "[w]hether or not the [prior art] systems were open or closed, it surely would [have been] obvious to try either in a reaction of the character defined by the patent."[43] The court further explained that "[i]f such is within the skill of the art, there can be no invention even though the results obtained by the claimed process are better than those shown by such art."[44]

In *In re Ruscetta*, the CCPA similarly held a method for electrolytically etching metals and alloys unpatentable in light of prior art disclosing the same method for etching the metal tantalum and a related method disclosing the claimed metals.[45] The court reasoned that because the claimed method was designed to etch a metal such as tantalum, "one would not be surprised if it etched the others."[46] The court concluded that "[c]ertainly it would [have been] obvious to try it."[47] Although the prior art may not have specifically pointed to the claimed invention, the obvious to try test developed in *Leum* and *Ruscetta* enabled courts to draw inferences from the prior art to invalidate patent claims.

Following the enactment of § 103 in the 1952 Patent Act, courts began to criticize the obvious to try test.[48] In *In re Huellmantel*, the CCPA addressed the obviousness of anti-inflammatory compositions that combined salicylate with either prednisone or prednisolone.[49] The solicitor asserted that because prednisone, prednisolone, or the combination of salicylate and cortisone was

40. *See, e.g.*, In re Ruscetta, 255 F.2d 687 (C.C.P.A. 1958); In re Leum, 158 F.2d 311 (C.C.P.A. 1946).

41. *Leum*, 158 F.2d at 311–12.

42. *Id.*

43. *Id.* at 312.

44. *Id.* (citing In re Kepler, 132 F.2d 130 (C.C.P.A. 1942)).

45. 255 F.2d at 692.

46. *Id.*

47. *Id.*

48. *See, e.g.*, In re Tomlinson, 363 F.2d 928, 931 (C.C.P.A. 1966); In re Huellmantel, 324 F.2d 998, 1000 (C.C.P.A. 1963).

49. *Huellmantel*, 324 F.2d at 1000.

known to treat inflammation, it was "obvious to at least try" to substitute prednisone or prednisolone for cortisone.[50] The court affirmed the rejection of the claims based on a different rationale, finding instead that the prior art suggested positive results from such combinations.[51] But the CCPA criticized the obvious to try test "insofar as it negates consideration of properties in determining obviousness under section 103, [it] flies in the face of the plain language of the statute."[52] The court continued: "Nothing is said about 'obvious to try.'"[53]

In *In re Tomlinson*, the CCPA echoed its skepticism in *Huellmantel*, further discrediting the obvious to try test.[54] Responding to an obvious to try argument, the CCPA held that obviousness under § 103 should be directed to compositions and methods, "not of the direction to be taken in making efforts or attempts."[55] Furthermore, the CCPA noted that "there is usually an element of 'obviousness to try' in any research endeavor" and the obvious to try test "would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of 'research.'"[56]

The Federal Circuit confronted the obvious to try test in *In re O'Farrell*.[57] The case concerned the validity of a biotechnology invention directed to producing a particular cloned gene in bacteria.[58] The prior art disclosed a method for producing a different gene in bacteria.[59] The court affirmed the obviousness rejection of the Board of Patent Appeals and Interferences (Board) because the claimed invention was obvious to try and the prior art suggested a "reasonable expectation of success."[60] The court explained that "[the prior art] contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful."[61]

But the Federal Circuit, like the CCPA in *Huellmantel* and *Tomlinson*, recognized the danger of the obvious to try test and advocated a narrow,

50. *Id.*
51. *Id.* at 1001.
52. *Id.* at 1001 n.3.
53. *Id.*
54. In re Tomlinson, 363 F.2d 928, 931 (C.C.P.A. 1966) (indicating that an obvious to try test would diminish the incentivizing effect of patents on research).
55. *Id.*
56. *Id.*
57. 853 F.2d 894, 902 (Fed. Cir. 1988).
58. *Id.* at 895.
59. *Id.* at 899–901.
60. *Id.* at 904.
61. *Id.* at 902.

limited, and cautious use of the approach.[62] The *O'Farrell* opinion emphasized that some inventions may be obvious to try, yet legally nonobvious, by describing two situations where courts misapplied the obvious to try test.[63] First, the court prohibited the use of the obvious to try test where success depends on trying many parameters or choices and the prior art does not indicate a preference for a particular parameter or choice.[64] Second, the obvious to try test is inappropriate where the prior art provides only general guidance for a particular approach or technology.[65] Furthermore, even if an invention is obvious to try, obviousness requires that the prior art provide a "reasonable expectation of success."[66] Obviousness, however, "does not require absolute predictability of success."[67]

1. A Biotechnology Primer

In the 1990s, the Federal Circuit, in two key decisions of *In re Bell*[68] and *Deuel*,[69] effectively shielded claims to the isolation and sequencing of genes from the obvious to try test. Before turning to those cases, this section provides a basic primer on gene cloning and biotechnology.

Proteins carry out essential cellular functions necessary for life, and protein deficiencies or aberrant activities cause many disorders. For example, proteins catalyze chemical reactions, transduce signals to coordinate biological processes, and provide components required for cellular architecture and movement.[70] Therapeutic proteins are a particular class of biopharmaceuticals. They can function as replacement therapies to treat protein deficiencies or as compositions designed to target a molecule or cell population that mediates a disease. Examples of such therapeutics include Epogen®, which treats erythropoietin deficiency in anemia;[71] Enbrel®, which blocks the inflammatory molecule Tumor Necrosis Factor (TNF) in

62. *See id.* at 903.
63. *Id.*
64. *Id.*
65. *Id.*
66. *Id.* at 904.
67. *Id.* at 903.
68. 991 F.2d 781, 781 (Fed. Cir. 1993) (holding that focusing on the methods of making the claimed sequences is misplaced).
69. 51 F.3d 1552, 1559 (Fed. Cir. 1995) ("'Obvious to try' has long been held to not constitute obviousness.").
70. *See, e.g.*, In re O'Farrell, 853 F.2d 894, 895–96 (Fed. Cir. 1988); BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 128–29 (3d ed. 1994).
71. *See, e.g.*, Pasquale F. Finelli & Matthew D. Carley, *Cerebral Venous Thrombosis Associated with Epoetin Alfa Therapy*, 57 ARCHIVES NEUROLOGY 260, 260 (2000).

rheumatoid arthritis;[72] and Herceptin®, which targets cancer cells expressing the receptor Human Epidermal growth factor Receptor 2 (HER2).[73]

Understanding the relationship between protein and deoxyribonucleic acid (DNA) enables researchers to make, use, and manipulate proteins—ultimately facilitating the development of therapies. Although the genetic code dictates what protein will arise from a given sequence of DNA,[74] knowledge of the polypeptide sequence of a protein does not conversely allow one to predict its corresponding DNA sequence.[75] Rather, gene cloning experiments are necessary to determine the polynucleotide sequence of the gene that encodes a particular protein of interest. Scientists have developed general laboratory methods that provide guidelines for a researcher to clone genes of interest.[76] Rarely, however, can a researcher fully adhere to such predefined methods. Biological systems are by their nature unpredictable. Conditions and procedures that were successful for cloning one gene may fail for another. Post-*Kubin*, a critical issue in evaluating obviousness is whether variations to established methods involve mere routine changes or require an inventive step.

Hereditary information is encoded in DNA as genes, and genes are transcribed from DNA to ribonucleic acid (RNA) and ultimately translated into a protein.[77] DNA is a polymer of units called nucleotides, each of which includes one of four bases: adenine (A), thymine (T), cytosine (C), and guanine (G).[78] Like DNA, RNA is a polymer of nucleotides but utilizes the base uracil (U) instead of thymine (T).[79] The order of the bases arranged along the sugar-phosphate backbone of DNA corresponds to the polynucleotide sequence.[80] This polynucleotide sequence directs the sequence of amino acids within a protein (its polypeptide sequence) through a two-step process. First, an RNA intermediate molecule known as messenger RNA

72. *See, e.g.*, George Spencer-Green, *Etanercept (Enbrel): Update on Therapeutic Use*, 59 ANNALS RHEUMATIC DISEASE 46, 46 (2000).

73. *See, e.g.*, Hiroji Iwata, *Perspective of Trastuzumab Treatment*, 14 BREAST CANCER 150, 150 (2007).

74. *See, e.g.*, *O'Farrell*, 853 F.2d at 897; ALBERTS, *supra* note 70, at 106.

75. *See infra* notes 83–88 and accompanying text.

76. If a complete genomic database is available, a person of skill in the art can identify all the polynucleotide sequences within the database that can specify a particular polypeptide sequence. The complete human genome has now been sequenced. Francis S. Collins et al., *A Vision for the Future of Genomics Research*, 422 NATURE 835, 835–36 (2003).

77. Francis Crick, *Central Dogma of Molecular Biology*, 227 NATURE 561 (1970).

78. *See, e.g.*, *O'Farrell*, 853 F.2d at 896; ALBERTS, *supra* note 70, at 4–5, 60.

79. *See, e.g.*, *O'Farrell*, 853 F.2d at 897; ALBERTS, *supra* note 70, at 60.

80. *See, e.g.*, *O'Farrell*, 853 F.2d at 896; ALBERTS, *supra* note 70, at 104.

(mRNA) is transcribed from the DNA template.[81] The mRNA then acts as a template for the assembly of amino acids during protein synthesis—a process called translation.[82]

A group of three bases, known as a codon, specifies the amino acid to be assembled into a protein during translation.[83] Sixty-four codons or 4^3 combinations are possible given that there are four bases and three positions within each codon, and these sixty-four codons code for the twenty natural amino acids and three stop signals.[84] The genetic code describes the relationship between codons and amino acids.[85] Because more than one codon can code for most amino acids, the genetic code is considered degenerate or redundant, though the genetic code has no ambiguity because each codon codes for only one amino acid.[86] For example, in mammals, six codons, UUA, UUG, CUU, CUC, CUA, and CUG, code for the amino acid leucine (Leu) and no other amino acid.[87]

Given a polynucleotide sequence of a gene with defined start and stop positions, one can precisely predict its corresponding polypeptide sequence by reading the codons, which map to specific amino acids. The degeneracy of the genetic code renders the reverse situation, determination of the precise polynucleotide sequence of a gene from its polypeptide sequence, impossible. For example, consider the following polynucleotide sequence, UUA UUG CUU CUC CUA CUG UUA. With knowledge from the genetic code that those codons encode Leu, it is straightforward to translate its polypeptide sequence as Leu-Leu-Leu-Leu-Leu-Leu-Leu. In contrast, consider the short polypeptide sequence: Leu-Leu-Leu-Leu-Leu-Leu-Leu. Because six codons can encode for Leu and there are seven Leu in the polypeptide, 6^7 or 279,936 combinations of codons can encode this polypeptide sequence. Given that proteins are large molecules, the number of possible polynucleotide sequences that can encode a given polypeptide sequence can be astronomical. For example over 10^{36} possible polynucleotide sequences could encode insulin-like growth factor, the relatively small protein of 79 amino acids at issue in *Bell*.[88] Thus, given only a polypeptide sequence of a protein, a

81. *See, e.g.*, *O'Farrell*, 853 F.2d at 897–98; ALBERTS, *supra* note 70, at 104–05.
82. *See, e.g.*, ALBERTS, *supra* note 70, at 106–08.
83. *See, e.g.*, *O'Farrell*, 853 F.2d at 897; ALBERTS, *supra* note 70, at 106.
84. *See, e.g.*, *O'Farrell*, 853 F.2d at 897; ALBERTS, *supra* note 70, at 106.
85. *See, e.g.*, *O'Farrell*, 853 F.2d at 897; ALBERTS, *supra* note 70, at 106.
86. *See, e.g.*, In re Deuel, 51 F.3d 1552, 1554 (Fed. Cir. 1995); ALBERTS, *supra* note 70, at 106.
87. *See, e.g.*, ALBERTS, *supra* note 70, at 106.
88. In re Bell, 991 F.2d 781, 784 (Fed. Cir. 1993).

scientist must successfully clone a gene in order to identify the corresponding gene sequence that encodes the protein.

Gene cloning commonly depends on screening of a complementary DNA (cDNA) library to identify the target cDNA that encodes the polypeptide in question.[89] A cDNA library contains a mixture of cDNAs generated from mRNAs isolated from a given tissue and thus represents the expressed genes within that tissue.[90] No library completely covers an entire genome or even all of the expressed genes within the starting tissue because genes are not ubiquitously expressed in all tissues or at all times, and conditions for creating a library vary in their ability to amplify particular targets.[91] The choice of tissue, culturing conditions, and amplification conditions represent a few of the many parameters that will alter the content of the library. A researcher knowing the biology of the target of interest, such as its expression profile, can make educated guesses to optimize some parameters and maximize the chances for coverage of the target gene. However, the unpredictability of physiological conditions suggests that even slight variations to the general protocols for library generation may significantly affect coverage. It is not possible to determine which parameters or combination of parameters will guarantee a library that contains the target gene. Notably, cloning will fail if the library does not contain the target.

Scientists employ various methods to isolate genes from libraries. For example, one method depends on screening of a library with a gene probe.[92] A gene probe is a DNA fragment whose sequence is designed to hybridize to a target gene sequence.[93] Given the polypeptide sequence of a protein, a scientist can design a probe with a higher probability of binding to the desired target. Another general approach involves expression cloning and screening, in which each cDNA of a library is expressed clonally, with each clone expressing one protein.[94] Screening leads to isolation of the clone exhibiting the property of interest. The property of interest can include a specific property possessed by the target protein, such as the ability to bind

89. *See, e.g.*, *Deuel*, 51 F.3d at 1554.

90. cDNAs are synthesized from mRNA in a process called reverse transcription and contain the coding sequences of a gene. *See, e.g.*, ALBERTS, *supra* note 70, at 310.

91. *See, e.g.*, J.G. Siedman, *Construction of Recombinant DNA Libraries*, *in* 68 CURRENT PROTOCOLS IN MOLECULAR BIOLOGY 5.0.1, 5.0.1–5.0.3 (Frederick M. Ausubel et al. eds., 2003).

92. *See, e.g.*, J.G. Siedman, *Screening of Recombinant DNA Libraries*, *in* 69 CURRENT PROTOCOLS IN MOLECULAR BIOLOGY 6.0.3, 6.0.3–6.0.5 (Frederick M. Ausubel et al. eds., 1994).

93. *See, e.g.*, *id.*; ALBERTS, *supra* note 70, at 312.

94. *See, e.g.*, Siedman, *supra* note 92.

an antibody probe, which is a type of protein that binds with great affinity to one specific molecule, or to activate a transcriptional response.

Knowing the polypeptide sequence of a protein, a scientist can develop methods to clone its corresponding gene. Although general screening methodology exists for gene cloning, scientists often use methods that diverge from the general protocol because each research endeavor can raise unique considerations. Each step may involve a separate experiment to optimize parameters and lead to failed attempts. Research, by its very nature, is empirical, yet may contain an element of the routine, because new discoveries often depend on prior discoveries.

2. The Federal Circuit Rejects the Obvious to Try Test

The Federal Circuit decisions in *Bell*[95] and *Deuel*[96] prohibited consideration of whether general methodologies to isolate genes made the claimed sequences obvious to try and therefore obvious. Instead, the Federal Circuit required that the prior art teach or suggest structurally similar polynucleotide sequences to support a finding of obviousness.[97]

In *Bell*, the Federal Circuit reversed the Patent Office's rejection of gene sequences as obvious because the prior art failed to teach or suggest the claimed sequences.[98] The case concerned the obviousness of polynucleotides encoding human insulin-like growth factors I and II (IGF-I and IGFF-II) in light of prior art disclosing the putative polypeptide sequences of IGF-I and IGF-II, and a general method for isolating a gene.[99] The court held that knowledge of the polypeptide sequences coupled with a general method for isolating a gene did not render the corresponding gene sequences obvious.[100] Although the court acknowledged that one could hypothesize the gene sequence based on knowledge of the protein sequence, the degeneracy of the genetic code meant that "a vast number of nucleotide sequences . . . might code for a specific protein."[101] Thus, "given the nearly infinite number of possibilities . . . the claimed sequences would not have been obvious."[102]

In *Deuel*, the Federal Circuit found claims to polynucleotide sequences encoding heparin binding growth factors (HBGFs) patentable because the

95. In re Bell, 991 F.2d 781, 784–85 (Fed. Cir. 1993).
96. In re Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995).
97. *Id.*
98. *Bell*, 991 F.2d at 784–85.
99. *Id.* at 782–83.
100. *Id.* at 784–85.
101. *Id.* at 784.
102. *Id.*

prior art did not disclose the claimed sequences.[103] The court reasoned that because polynucleotides were chemical entities, a prima facie case of obviousness required that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art.[104] Although the prior art described a general method for isolating a gene and partial polypeptide sequences for heparin-binding brain mitogens that were identical to a portion of the applicant's polypeptide sequences,[105] the prior art failed to suggest the claimed polynucleotide sequences.[106] Thus, the court found that the claims were not obvious.[107]

The court also addressed the obvious to try argument and stated that "the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious."[108] Focusing on the direction of research under the obvious to try test was flawed because a "general motivation to search for some gene" did not necessarily make obvious a gene that was subsequently obtained as a result of that search.[109] Furthermore, basing a rejection on what "one might have been motivated to try to do . . . amounts to speculation and an impermissible hindsight."[110] Finally, the court explicitly rejected the obvious to try test as it "has long been held not to constitute obviousness."[111]

These decisions recognized the complexity and unpredictable nature of biotechnology inventions, including those involving gene sequences, and insulated such inventions from obviousness attacks based on obvious to try. But *KSR* and *Kubin* have changed the patent landscape for these inventions.

II. *IN RE KUBIN*

A. BACKGROUND

Kubin concerned a patent application claiming the polynucleotide sequence of a gene encoding NAIL, a protein expressed on a class of lymphocytes important in tumor and viral immunity called Natural Killer

103. In re Deuel, 51 F.3d 1552, 1558–59 (Fed. Cir. 1995).
104. *Id.* at 1558.
105. *Id.* at 1556.
106. *Id.* at 1558.
107. *Id.* at 1560.
108. *Id.* at 1559.
109. *Id.* at 1558.
110. *Id.*
111. *Id.* at 1559.

(NK) cells.[112] NAIL modulates NK cell function in part through its binding interactions with a protein called CD48.[113] Methods of using NAIL or its gene sequence could provide therapeutic value by altering NK cell function and immune responses.[114] The Examiner rejected the claims as obvious in light of three references: a patent disclosing a human NAIL-specific antibody and a prophetic method of screening a NK cell library with the antibody ("Valiante reference"); a general cloning manual ("Sambrook reference"); and a scientific article disclosing murine NAIL, a murine NAIL-specific antibody, and a method for cloning the gene encoding the murine NAIL ("Mathew reference").[115]

B. THE BOARD'S DECISION

The Board sustained the Examiner's rejection of the claims for obviousness because a person of ordinary skill in the art had a reasonable expectation of success in cloning the NAIL polynucleotide with conventional methods.[116] First, the Board found as a factual matter that the applicants used the same methodologies as those of the Valiante and Sambrook references to isolate the gene that encodes NAIL.[117] Second, the Board found that the state of the art had "advanced significantly" during the period between the filing dates of the *Deuel* and *Kubin* applications.[118] Third, the Board noted that *KSR* cast doubt on the viability of *Deuel*'s rejection of the obvious to try test.[119] Fourth, the Valiante reference provided a "reasonable expectation of success" in obtaining the claimed polynucleotide sequence.[120] Thus, contrary to the precedents set forth in *Bell* and *Deuel*, which held that conventional methodologies are irrelevant in an obviousness determination, the Board found that the use of conventional methodologies to isolate the NAIL polynucleotide rendered the invention obvious.[121]

A reference that teaches away from a claimed invention may help establish nonobviousness of that invention.[122] A reference teaches away when

112. In re Kubin, 561 F.3d 1351, 1352 (Fed. Cir. 2009).
113. *See id.* at 1353.
114. *See id.* at 1353–55.
115. *Id.* at 1354.
116. Ex parte Kubin, 83 U.S.P.Q.2d (BNA) 1410, 1413–15 (B.P.A.I. 2007).
117. *Id.* at 1413.
118. *Id.*
119. *Id.* at 1414.
120. *Id.* at 1413.
121. *See id.* at 1414 (holding that NAIL cDNA is not patentable because it would have been obvious to isolate it).
122. *See, e.g.*, In re Kubin, 561 F.3d 1351, 1357 (Fed. Cir. 2009) (discussing a reference that fails to support nonobviousness because it fails to teach away).

it would deter a person of ordinary skill "from following the path set out in the reference."[123] The degree of teaching away depends on the particular facts. The Board found that this doctrine did not apply to the Mathew reference.[124] Even though the Mathew reference questioned the existence of a human version of NAIL, it "merely indicate[d] that conflicting data existed" regarding the existence of human NAIL rather than teaching away.[125]

C. THE FEDERAL CIRCUIT'S DECISION

On appeal, the Federal Circuit affirmed the Board's obviousness rejection because the invention was obvious to try and the prior art provided a reasonable expectation of success.[126] The crux of the decision addressed the viability of the holdings in *Deuel*. Under *Deuel*, the *Kubin* claims would likely be patentable because the prior art did not disclose structurally similar sequences and despite knowledge of the protein, general methods for gene cloning would not render the corresponding gene sequence obvious. Furthermore, under *Deuel*, obvious to try is an inappropriate test for obviousness.[127]

Agreeing with the Board's skepticism about *Deuel*'s continuing vitality, the court overruled *Deuel*, citing *KSR* for "unambiguously discredit[ing]" the holding that "the obviousness inquiry cannot consider that the combination of the claim's constituent elements was 'obvious to try.'"[128]

The court then resurrected its own *O'Farrell* decision.[129] The *O'Farrell* court had identified two situations where what is obvious to try is nonetheless not obvious.[130] The first situation occurs when success depends on trying numerous possibilities but where the prior art failed to indicate the parameters or choices that would likely lead to success.[131] The court explained that in this situation, courts should not succumb to hindsight since the inventor "merely throws metaphorical darts at a board filled with combinatorial prior art possibilities."[132] The court found support in *KSR*, which held that the inverse situation, "where a skilled artisan merely pursues

123. *Id.*
124. Ex parte Kubin, 83 U.S.P.Q.2d (BNA) 1410, 1414 (B.P.A.I. 2007).
125. *Id.*
126. In re Kubin, 561 F.3d at 1361.
127. *Id.* at 1358 (citing In re Deuel, 51 F. 3d 1552, 1559 (Fed. Cir. 1995)).
128. *Id.*
129. *Id.* at 1359–60.
130. *Id.*
131. *Id.* at 1359.
132. *Id.*

'known options' from a 'finite number of identified, predictable solutions,'" was obvious.[133]

The second situation occurs when the prior art provides only general guidance for a particular approach or technology.[134] Again, the court found support for this in *KSR* where the Court stated that "§ 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'"[135]

The court held that these situations did not apply to the claims in *Kubin*.[136] The court also held that any putative differences between the Valiante and Sambrook references and Kubin's methods of deriving the claimed polynucleotide were irrelevant.[137] The record showed that the Valiante reference's prophetic example would "produce for any person of ordinary skill in this art the claimed polynucleotide."[138] Moreover, the court noted that appellants had in fact used the conventional techniques taught by the Valiante and Sambrook references to isolate the NAIL polynucleotide.[139] The court also highlighted the appellants' own disclosure referring to the Sambrook reference, which undermined arguments that the reference was deficient.[140] Because the appellants had argued that Sambrook's standard biochemical methods could lead to their claimed sequence, the court refused to allow them to discount the reference's relevance to the obviousness of their claims.[141]

Like the Board, the court also refused to consider Mathew as a reference that teaches away.[142] The court found that Mathew's "quasi-agnostic stance"[143] regarding the existence of a human version of NAIL would not have discouraged but instead "aroused a skilled artisan's curiosity"[144] to pursue cloning of NAIL.

The court concluded that because the prior art disclosed NAIL, a motivation to isolate the gene encoding NAIL, and instruction to use an antibody specific to NAIL to clone the gene, "a skilled artisan would have

133. *Id.* (quoting KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007)).
134. *Id.* at 1359–60.
135. *Id.* (quoting *KSR*, 550 U.S. at 417).
136. *Id.* at 1361.
137. *Id.* at 1356.
138. *Id.*
139. *Id.*
140. *Id.*
141. *Id.*
142. *Id.* at 1357.
143. *Id.*
144. *Id.*

had a resoundingly 'reasonable expectation of success' in deriving the claimed invention in light of the teachings of the prior art."[145] The court also refused "to cabin *KSR* to the 'predictable arts' (as opposed to the 'unpredictable art' of biotechnology)."[146] The court therefore affirmed the Board's finding of invalidity because "the claimed invention was reasonably expected in light of the prior art and 'obvious to try.'"[147]

III. DISCUSSION

A. A NEW OBVIOUSNESS STANDARD

In *Kubin*, the Federal Circuit set a new standard for obviousness—overturning its own precedent in *Deuel* and branding a gene sequence as unpatentable because its cloning was obvious to try and had a reasonable expectation of success.[148] The court relied on *KSR* and *O'Farrell* to conclude that the invention was obvious to try[149] and also rejected the *Deuel* standard requiring structural similarity in the prior art to show obviousness of a gene sequence.[150] Furthermore, the court extended the obvious to try test to the unpredictable art of biotechnology.[151]

1. Kubin *Expands* KSR*'s Obvious to Try Test*

In *KSR*, the Supreme Court invalidated an invention directed to a combination of elements in the mechanical arts. The Court based its reasoning primarily on three of its precedents, all of which involved combinations of prior art mechanical elements.[152] First, the Court cited *United States v. Adams*, which concerned the patentability of a "wet battery."[153] The Court discussed *Adams*, a companion case to *Graham*, for its holding that combinations of prior art structures must do more than yield a predictable result to be patentable.[154] Second, the Court cited *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, which involved a road-paving machine attached to a patented burner.[155] In *Anderson's-Black Rock*, the Court found a combination

145. *Id.* at 1360.
146. *Id.* at 1360–61.
147. *Id.* at 1361.
148. *Id.* at 1358, 1361.
149. *Id.* at 1358–60.
150. *Id.* at 1358–59.
151. *Id.* at 1360–61.
152. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 416–17 (2007).
153. *Id.* at 416 (citing United States v. Adams, 383 U.S. 39 (1966)).
154. *Id.*
155. *Id.* at 416–17 (citing Anderson's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57 (1969)).

of old elements unpatentable because it "added nothing to the nature and quality" of the prior art.[156] Third, the Court cited *Sakraida v. Ag Pro, Inc.*, a case concerning a claim for a water flush system to remove dairy floor debris.[157] In *Sakraida*, the Court concluded that a rearrangement of old elements that yielded only expected results was obvious.[158] After describing the obviousness principles set forth in those mechanical cases, the Court criticized rigid application of the TSM test[159] and cited to *Deuel* solely to point out the Federal Circuit's view that "'[o]bvious to try' has long been held not to constitute obviousness."[160] The Court explained that the Federal Circuit erred because an invention might be obvious if it was obvious to try.[161]

It is difficult to determine whether the Court intended that obvious to try should apply to biotechnology or that the obviousness rules developed from the mechanical cases of *Adams*, *Anderson's-Black Rock*, and *Sakraida* would translate to the facts in *Kubin*. The Court explained in *KSR* that its prior cases were instructive when the obviousness inquiry involves the combination of prior art elements.[162] Unlike *KSR*, *Kubin* involves a complex and unpredictable technology and did not merely combine known prior art structural elements.

In *Kubin*, the Federal Circuit interpreted *KSR* expansively to support using the obvious to try test to evaluate the obviousness of polynucleotide sequences. Under *KSR*, reason to pursue known options exists "when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions."[163] The Board differed, finding motivation to pursue options when "there [are] a limited number of methodologies."[164] The Federal Circuit affirmed the reasoning of the Board's decision.[165] *KSR* dealt with the combination of known structural elements in the mechanical arts, not the use of existing methods to create a new invention from known elements. By equating "solutions," which referred to structural elements, with "methodologies" or the direction of research, the

156. *Id.*
157. *Id.* at 417 (citing Sakraida v. Ag Pro, Inc., 425 U.S. 273 (1976)).
158. *Id.*
159. *Id.* at 419–22.
160. *See id.* at 414 (alteration in original) (quoting Teleflex, Inc. v. KSR Int'l. Co., 119 F. App'x 282, 289 (Fed. Cir. 2005), *rev'd*, 550 U.S. 398 (quoting In re Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995))).
161. *Id.* at 421.
162. *Id.* at 417.
163. *Id.* at 421.
164. Ex parte Kubin, 83 U.S.P.Q.2d (BNA) 1410, 1414 (B.P.A.I. 2007).
165. In re Kubin, 561 F.3d 1351, 1360–61 (Fed. Cir. 2009).

Federal Circuit broadened the scope of prior art that may render a patent obvious under the obvious to try test.

2. Structural Similarity Is No Longer Required to Show Obviousness

Kubin also set a new standard for gene patents because structural similarity is no longer required to show obviousness of polynucleotide sequences. For new chemical compositions, "a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound."[166] In *Bell* and *Deuel*, the Federal Circuit applied this standard to polynucleotide sequences.[167] But in *Kubin*, the Federal Circuit refused to require structural similarity to support obviousness of polynucleotide sequences.

Like *Bell* and *Deuel*, *Kubin* concerned the validity of gene sequences in light of prior art teaching the encoded protein and a general cloning manual. Unlike in *Bell* and *Deuel*, in *Kubin*, the prior art did not disclose either the complete or partial polypeptide sequence of the protein at issue.[168] Instead, the prior art disclosed a probe specific for the protein and a prophetic method for isolating the gene encoding the protein.[169] Thus, the prior art in *Kubin* provided less information on the polypeptide sequence encoded by the claimed gene than the corresponding prior art in *Bell* and *Deuel*. Furthermore, like in *Bell* and *Deuel*, the prior art in *Kubin* did not disclose structurally similar polynucleotide sequences, and under *Bell* and *Deuel*, conventional methods for gene cloning are irrelevant in the obviousness analysis.[170] Therefore, if *Bell* and *Deuel* remained good law, the Federal Circuit should have found the *Kubin* claims nonobvious.

The structural similarity standard makes sense for chemical compounds where a showing of obviousness requires a motivation to modify the prior art to arrive at the new compound. Evidence that the prior art failed to disclose a compound structurally similar to the claimed compound would help establish nonobviousness. Polynucleotides are chemical compositions. Basing their obviousness on the structural similarity standard is consistent with how biotechnology research proceeds. Scientists have been characterizing proteins since well before current methods of genetic engineering existed, and even now researchers are motivated to clone a specific gene because its encoded

166. *See, e.g.*, Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007) (citing In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995)).

167. *Deuel*, 51 F.3d at 1558; In re Bell, 991 F.2d 781, 784 (Fed. Cir. 1993).

168. In re Kubin, 561 F.3d at 1354 (stating that the Valiante reference does not disclose the polypeptide sequence of NAIL).

169. *Id.* at 1354–55.

170. *Deuel*, 51 F. 3d at 1559; *see Bell*, 991 F.2d at 784–85.

protein mediates a biologically important process. If mere knowledge of a protein in the prior art and a general guideline for cloning renders the corresponding gene sequence obvious, whole classes of genes would be unpatentable.

On the other hand, the structural similarity standard may be inappropriate for evaluating the obviousness of gene sequences. A researcher generally does not identify a gene sequence by looking to structurally similar compositions in the prior art as he would for standard chemical compounds. Instead, a researcher often relies upon the relationship between protein and DNA to clone the gene. Under the *Deuel* standard, virtually all gene patents would be valid because general methods are irrelevant to the obviousness of a polynucleotide sequence in the absence of prior art suggesting the claimed sequence. The *Kubin* holding that courts can consider methodologies in the obviousness inquiry significantly changes the obviousness standard for genes.

B. A REASONABLE EXPECTATION OF SUCCESS

Under *KSR*, an obvious to try solution must lead to "anticipated success."[171] In *Kubin*, the Federal Circuit interpreted "anticipated success" to mean "reasonable expectation of success."[172] Courts view this reasonable expectation of success from the perspective of an ordinary person of skill in the art, and obviousness does not require "absolute predictability of success."[173]

The two impermissible obvious to try situations described in *O'Farrell* help determine whether an invention is reasonably expected.[174] The *O'Farrell* exceptions protect efforts to solve problems where the prior art only suggests success among impractically large numbers of possibilities or general success in a field with many approaches. Success in those situations would clearly result from technological innovations. Thus, a patentability standard requiring that obvious to try inventions fall within the two *O'Farrell* exceptions rewards inventions that promote the progress of science and the useful arts. Yet, such a stringent obvious to try test may lapse back to the discredited "flash of creative genius" standard.

A pivotal question in *Kubin* was whether the prior art provided a reasonable expectation of success. In *Kubin,* the court found that the prior art taught "the protein of interest, a motivation to isolate the gene coding for that protein, and illustrative instructions to use a monoclonal antibody

171. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).
172. In re Kubin, 561 F.3d at 1361.
173. *Id.* at 1360 (citing In re O'Farrell, 853 F.2d 894, 903–04 (Fed. Cir. 1988)).
174. *Id.* at 1359–60.

specific to the protein for cloning this gene."[175] The court also found that appellants used conventional methods.[176] Therefore, the prior art provided teachings that would have led to a "reasonable expectation of success."[177]

If in fact the *Kubin* methods were identical to the illustrative instructions provided in the prior art or were conventional, the invention may have been obvious to try. Yet whether the *Kubin* technology followed a predictable path is not clear because the court ignored the differences between the prior art and the appellants' methods. In fact, the court even stated that "any putative difference in Valiante's/Sambrook's and appellants' *processes* does not directly address the obviousness" of the claimed gene sequences.[178]

The court's conclusion that there was a reasonable expectation of success provides an unsatisfying explanation for how to evaluate obviousness, because the extent to which the prior art taught or suggested the *Kubin* methods and to what extent the *Kubin* methods were conventional remains unclear. The prior art references in *Kubin* described general guidelines for cloning a gene and a method for isolating the gene using an antibody to screen an NK cell library.[179] Appellants isolated the claimed gene using the same antibody and followed general guidelines in the prior art. Although the appellants' methods and the prior art methods were similar, they differed in at least one major way. The prior art disclosed an NK cell library but failed to disclose how to make the NK cell library, the starting material for the screening process.[180]

If the prior art taught a method of screening a library but failed to teach or suggest that library, the gene sequences might be nonobvious because there would be no reasonable expectation of success. The appellants argued that the development of their NK cell library was "remarkable" and involved isolating pooled RNAs from both resting NK cells and NK cells stimulated with various activators.[181] If there were an impracticably large number of possible ways to generate the library or the prior art provided only general guidance for the library, the *O'Farrell* exceptions might render the invention nonobvious. While general knowledge of how to make an NK cell library existed within the prior art, how much the appellants' method of making the NK cell library deviated from those known methods is not discernible and

175. *Id.* at 1360.
176. *Id.*
177. *Id.* at 1355.
178. *Id.* at 1356.
179. *Id.* at 1354–55.
180. Corrected brief of In re Marek Z. Kubin and Raymond G. Goodwin at 13, In re Kubin, 561 F.3d 1351 (Fed. Cir. 2009) (No. 2008-1184).
181. *Id.* at 16.

those deviations from the prior art determine whether a reasonable expectation of success existed.

Within the unpredictable arts, researchers often vary admittedly predictable and routine procedures. Whether these variations represent innovation or merely ordinary skill is a complex question that harkens back to the *Graham* standard of obviousness. Despite the apparent objectivity provided by the obviousness standard, the standard suffers from multiple layers of subjectivity and depends on the point of view and knowledge of the ordinary person skilled in the art. Courts will likely struggle to determine what weight should be given to the existence of unpredictability in the art when an invention results from methods that to some extent rely on conventional methods.

C. *KUBIN* CREATES UNCERTAINTY FOR BIOTECHNOLOGY

The potential impact of *Kubin* on the validity and patentability of gene sequence claims causes apprehension in the biotechnology field.[182] Obviousness challenges may invalidate many gene patents if the protein was known and gene cloning depended on routine methods. Biotechnology patents often cite the Sambrook reference, likely in order to satisfy the enablement requirement,[183] and this may, as in *Kubin*, undermine potential nonobviousness arguments. After *Kubin*, future biotechnology patent applicants should cautiously cite the Sambrook reference or other standard manuals, and balance the need for an enabling disclosure with the need to show the nonobviousness of their invention. In situations where less was known about the encoded protein, where applicants or patentees can provide evidence of failed attempts, or where non-routine methods contributed to cloning, the inventions may survive a nonobviousness challenge based on *Kubin*. One commentator, however, noted that the impact of *Kubin* might be less severe than initially feared because most of the known genes have been cloned and patented, and a substantial number of those patents are likely near the end of their patent term.[184]

Innovation in biotechnology provides many social benefits, most notably in the area of human health. Patents play a vital role in encouraging investment in biopharmaceutical and biotechnological research. Before a

182. *See, e.g.*, Dennis Crouch, *In re Kubin: Federal Circuit Expands Obvious-To-Try Jurisprudence*, PATENTLY-O, Apr. 7, 2009, http://www.patentlyo.com/patent/2009/04/in-re-kubin-federal-circuit-expands-obvious-to-try-jurisprudence.html.

183. 35 U.S.C. § 112 (2006).

184. Kevin E. Noonan, *In re Kubin (Fed. Cir. 2009)*, PATENT DOCS: BIOTECH & PHARMA PATENT LAW & NEWS BLOG, Apr. 5, 2009, http://www.patentdocs.org/2009/04/in-re-kubin-fed-cir-2009.html.

typical investment generates significant returns, however, most biotechnology innovations undergo a lengthy development process that incurs significant financial costs.[185] During preclinical development, researchers evaluate candidate therapies for suitability for human testing in clinical trials. Clinical trials are divided into three phases: Phase I, II, and III, with each phase characterizing various aspects of the therapy's safety and efficacy. The public cannot access these therapies until after the Food and Drug Administration (FDA) approves the therapy.[186] A recent study estimated the magnitude of research and development costs for biopharmaceuticals based on specific-drug cost, development time, and clinical success rate.[187] It found that development of biopharmaceuticals takes an average of 12.5 years from initial investment to final approval.[188] Furthermore, this same study noted that total capitalized costs per approved biopharmaceutical could be as high as $1.241 billion[189] with an overall clinical approval success rate of 30%.[190]

Without the protection of patents, biotechnology researchers may be deterred from pursuing costly, high-risk research projects.[191] In fact, companies routinely screen and eliminate potential programs with inadequate patent protection.[192] Empirical studies also show that patents play roles in securing investment and financing for start-ups, and that increased patenting by venture-backed companies in the biotechnology industry is correlated with investment.[193]

185. *See, e.g.*, Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 471 (2007).

186. Biopharmaceuticals, like pharmaceuticals, cannot benefit the public without FDA approval. *See* Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 505 (2009).

187. DiMasi & Grabowski, *supra* note 185, at 470.

188. *Id.* at 475.

189. *Id.*

190. *Id.* at 472.

191. *See, e.g.*, Roin, *supra* note 186, at 504 (noting wide acceptance that patents play essential roles in motivating pharmaceutical research and development).

192. *See id.* at 513 (citing BERNICE SCHACTER, THE NEW MEDICINES: HOW DRUGS ARE CREATED, APPROVED, MARKETED, AND SOLD 52 (2006); C. Merle Crawford, *Defining the Charter for Product Innovation*, *in* GENERATING TECHNOLOGICAL INNOVATION 165, 175 (Edward B. Roberts ed., 1987); Peter Gwynne & Gary Heebner, *Protecting the Assets*, 297 SCIENCE 2083, 2086 (2002); Lester A. Mitscher & Apurba Dutta, *Contemporary Drug Discovery*, *in* 1 DRUG DISCOVERY AND DEVELOPMENT 103, 115 (Mukund S. Chorghade ed., 2006)).

193. Stuart J.H. Graham & Ted Sichelman, *Why do Start-ups Patent?*, 23 BERKELEY TECH. L.J. 1063, 1078 (2008); *see* Ronald J. Mann & Thomas W. Sager, *Patents, Venture Capital, and Software Start-ups*, 36 RES. POL'Y 193, 205 (2007) (stating that it is unclear if the correlation is due to a causal relationship).

Although patents may provide valuable incentives for researchers and investors to pursue lines of research, patents can also stifle innovation. Gridlock can result when too many patent owners hold rights to discoveries and block others from building on those discoveries.[194] Patent-related licensing barriers and transaction costs may also hinder research.[195] Moreover, rewarding researchers for merely incremental innovations would contradict the policies underlying the patent system, and lower standards of patentability could deter investment in riskier and innovative research.

In sum, whether a biotechnology invention should be patentable presents a difficult question. Biotechnology inventions often depend on researchers using a proven set of tools while methodically varying parameters, and much research consequently involves an element of "obviousness to try." Because *Kubin's* obvious to try standard attacks the method of making an invention, it threatens lines of research that logically follow from a discovery. For example, scientists may use established methods to insert a gene into a cell line to express a purified protein that may one day be of therapeutic value. Courts may find that those methods, the cell lines, or the protein products are unpatentable as "obvious to try." *Kubin* also brings into question other areas of research that utilize established methods. For example, patents for antibody therapeutics, such as Enbrel® and Herceptin® or as yet undeveloped therapies, may be vulnerable because methods for generating them have become routine. If similar new therapies are obvious, investors might avoid the costly research and development efforts required to bring them to market, thereby depriving the public of access to these inventions.

IV. CONCLUSION

Kubin overruled key holdings in *Deuel* by finding that conventional methodologies for gene cloning might preclude patent protection for gene sequences and that the obvious to try test applies to the unpredictable art of biotechnology. Although the Federal Circuit did not state that polynucleotide sequences are obvious *per se*, its holding effectively lowered the bar for finding gene patents obvious.

Advances in biotechnology often build upon basic methods, with research proceeding in incremental steps. Because obvious to try focuses on the methods of discovery, the plodding and stepwise exploration of new

194. Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 698–99 (1998).

195. *See, e.g.*, *id.* at 699; Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting*, *in* 1 INNOVATION POLICY AND THE ECONOMY 119, 119–22 (Adam B. Jaffe et al. eds. 2001).

areas in biotechnology research and development may not show the inventive step required to satisfy the nonobviousness requirement. These methods may involve great effort and costs, and provide many social benefits. *Kubin* employs a stringent standard to evaluate obviousness, and application of this high standard may retard investment in biotechnology. Obviousness standards that account for the complexity, unpredictability, and costly nature of biotechnology are crucial to promote the investment and risk-taking necessary to drive innovations in the field.