

**INNOVATION VS. EVASION:
CLARIFYING PATENT RIGHTS IN
SECOND-GENERATION GENES AND PROTEINS**

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ABSTRACT

“Protein engineering” enables molecular biologists to create modified proteins with properties different from those found in nature. These “second generation” proteins present both promise and peril for the biotechnology industry. On the one hand, an increasing number of pharmaceutical products contain modified proteins, many with important clinical advantages. These innovative products should not be blocked by patents on the natural gene or protein. On the other hand, companies can now create modified proteins that behave no differently from the patented analogs in their competitors’ products. This threatens to make gene and protein patents so easy to evade as to render them almost meaningless.

This Article examines the patent-law question posed by protein engineering: do patents on genes and proteins cover second-generation analogs? Gene and protein patents are usually construed narrowly enough that infringement is governed by the doctrine of equivalents. Unfortunately, the case law does not satisfactorily explain how to determine whether a modified gene or protein is equivalent to its natural analog.

In this Article, the authors propose using the “known interchangeability” test to analyze infringement by second-generation genes and proteins under the doctrine of equivalents. The known interchangeability test, unlike alternatives such as the function-way-result test, is an objective measure of the functional similarities or differences between the patented and accused products. The authors contend that the known interchangeability test therefore strikes the right balance between innovation and evasion.

I. INTRODUCTION

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The recent sequencing of the human genome has generated considerable debate over the patentability of naturally occurring human genes. The issue has received attention at the highest political levels,¹ and the United States Patent and Trademark Office (PTO) has reacted by issuing new guidelines for the review of patents on genes.² But the remarkable scientific accomplishment represented by the Human Genome Project is just the first step toward clinical application of that knowledge.

At the outset, medical breakthroughs will require the identification and characterization of the proteins expressed by human genes.³ Going further, in some cases scientists will be able to create modified proteins with properties superior to those of their naturally occurring analogs. This process of "protein engineering" involves altering the nucleotide sequence of the gene so it expresses a protein with a different amino acid sequence, which in turn may alter the protein's properties.⁴ Such "second generation" proteins are an important and growing segment of the biopharmaceutical market, and in some cases may yield important clinical advantages over their natural analogs.

The potential utility and value of these engineered proteins raises a question less visible than the patentability of human genes, but scarcely less important for the pharmaceutical industry: whether gene and protein patents, once issued, will cover variant genes and proteins that differ slightly in their nucleotide or amino acid sequence. On the one hand, such dominance would be undesirable if it impeded the development of clinically superior second-generation proteins. On the other hand, the increasing ease of protein engineering raises the spectre that all gene and protein patents could be easily evaded by making slight variations to the nucleotide or amino acid sequence. Thus, defining a clear and sensible boundary as to when a natural-sequence patent may dominate second-generation analogs will be critical to pharmaceutical companies' continuing ability to

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1. *See, e.g.*, Remarks on Completion of the First Survey of the Human Genome Project, 36 WEEKLY COMP. PRES. DOC. 1499 (July 3, 2000) (statement of President Clinton); *Gene Patents and Other Genomic Inventions: Hearing Before the Subcomm. on Courts and Intellectual Property of the House Comm. on the Judiciary*, 106th Cong. (2000).
 2. *See* Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001); Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001).
 3. *See, e.g.*, Stanley Fields, *Proteomics in Genomeland*, 291 *Science* 1221 (2001); Carol Ezzell, *Beyond the Human Genome*, *SCI. AM.*, July 2000, at 64; Andrew Pollack, *The Next Chapter in the Book of Life Is Written in the Proteins*, *N.Y. TIMES*, July 4, 2000, at F1.
 4. For background on protein engineering, see Part II below.

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invest in the development of recombinant DNA products. That boundary, however, is not yet clear.

The issue generally arises in two ways. First, the discoverer of a natural sequence may apply for a patent that encompasses analogs within its literal claim scope—either by claiming all genes or proteins with a certain structural similarity or by claiming sequences based on the protein's function. Once issued, such a broad patent can be challenged in infringement litigation for lack of enablement or written description. Second, the holder of a narrower patent to the natural sequence may claim that the second-generation gene or protein, although outside the literal claim scope, infringes the patent under the doctrine of equivalents. At present, it is unclear how courts will decide whether the two gene or protein sequences are equivalent.

The difficulties often created when radically new technology is forced into existing patent-law categories are here compounded by the fact that some of the underlying patent law doctrines have recently become unsettled. Earlier this year, in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*,⁵ the Supreme Court upheld the doctrine of equivalents by rejecting the Federal Circuit's expansive application of prosecution history estoppel, which threatened to preclude any finding of equivalence for most patents. More recently, in *Enzo Biochem, Inc. v. Gen-Probe Inc.*,⁶ the Federal Circuit re-affirmed its precedent on the application of the written description doctrine to gene patents, but applied that precedent in a manner that renders uncertain when a person who discovers a gene may obtain claims to analog sequences.

In this article, we propose an analytical framework for determining whether variant nucleotide or amino acid sequences infringe patents covering their natural analogs. In Part II, we review briefly the background principles of protein engineering and patent law. In Part III, we analyze the existing case law. The most significant precedent is *Genentech, Inc. v. Wellcome Foundation Ltd.*,⁷ the only case in which the Federal Circuit has ruled on (and, in that case, rejected) a claim that a second-generation protein infringed a patent on a naturally occurring protein. Unfortunately, *Genentech* offers limited guidance to infringement analyses with different fact patterns.

5. 535 U.S. 722 (2002).

6. 296 F.3d 1316 (Fed. Cir. 2002) (panel opinion on petition for rehearing). The opinions on denial of a petition for rehearing en banc can be found at 42 Fed. Appx. 439 (Fed. Cir. 2002).

7. 29 F.3d 1555, 1569 (Fed. Cir. 1994).

In Part IV, we attempt to reconcile the case law on the patentability of claims that encompass gene or protein sequences that the inventor never actually created. We suggest that the patentability of such claims depends on the state of knowledge concerning how changes to a nucleotide or amino acid sequence affect the function of the resulting protein. Given the present state of the art, we conclude that, in most cases, claims literally covering variant sequences are not patentable. As a result of this conclusion, we believe that some form of the doctrine of equivalents is necessary to provide meaningful protection to gene and protein patents. It is equally important, however, that the doctrine not extend too far and read on variant genes and proteins with substantially improved properties.

In Part V, we propose a framework for the doctrine of equivalents in the area of protein engineering. Unfortunately, the existing case law on the application of the doctrine of equivalents to gene or protein patents is analytically rough at best, providing poor tools for judges to resolve the hard cases to come, and making it impossible for lawyers to advise their clients of probable outcomes with any confidence. We identify one thread from the existing precedent—the “known interchangeability” test—that can and should be developed into a reasonably clear rule of discrimination.⁸ We also discuss why some other approaches to equivalence found in the case law or in academic commentary can only create confusion if applied to gene and protein patents.

II. BACKGROUND

The properties of a protein are largely defined by the protein’s amino acid sequence. The three-dimensional structure (or “conformation”) of a protein determines its biological and chemical properties. And, with few qualifications, the amino acid sequence determines the specific three-dimensional structure into which the protein folds. Thus, “function is derived from three-dimensional structure, and three-dimensional structure is specified by the amino acid sequence.”⁹

The amino acid sequence of a protein is in turn defined by the nucleotide sequence in the gene that codes for that protein. More than one nu-

8. Cf. Paul R. Michel, *The Role and Responsibility of Patent Attorneys in Improving the Doctrine of Equivalents*, 40 IDEA 123, 129 (2000) (urging that “the notion of ‘known interchangeability’ . . . be developed from a mere factor in a list of criteria to a true test”).

9. HARVEY LODISH ET AL., *MOLECULAR CELL BIOLOGY* 51 (4th ed. 2000); see also BRUCE ALBERTS ET AL., *MOLECULAR BIOLOGY OF THE CELL* 111-13 (3d ed. 1994); THOMAS E. CREIGHTON, *PROTEINS: STRUCTURES AND MOLECULAR PROPERTIES* 31 (2d ed. 1993).

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cleotide sequence can code for the same amino acid sequence, due to the redundancy of the genetic code, but a given nucleotide sequence is translated into a single amino acid sequence.¹⁰

In nature, individual organisms may have a gene with a nucleotide sequence slightly different from the normal gene for that species—a variation known as an “allele.” Some such genetic variations are “silent”—that is, they result in no change to the amino acid sequence of the protein. Others result in amino acid changes, sometimes with no effect on the properties of the protein, but in other cases resulting in significant loss of biological activity. A number of serious, and even fatal, genetic diseases in humans are caused by the mutation of a single nucleotide.¹¹

Since the early 1980s, researchers have had the ability to artificially modify genes. The 1993 Nobel Prize in Chemistry was awarded to Michael Smith for his invention of the technique of site-directed mutagenesis, the technique now commonly used to make targeted changes to the nucleotide sequence of a gene.¹² Such genetic mutations may, by design, result in changes to the amino acid sequence of the encoded protein, thus creating “muteins”—proteins not known to occur in nature. Protein engineering, the science of designing and creating muteins, is now an important area of research.¹³

At present, the capabilities of protein engineering are significantly limited because, while scientists can change a protein sequence with precision, they normally cannot know in advance the resulting effects (if any) on the biological and chemical properties of the protein. “It is presently not possible . . . to deduce reliably the three-dimensional folded structure of a protein from its amino acid sequence, and without knowing its detailed folded structure, it is not possible to understand the molecular basis of a protein’s function.”¹⁴ Thus, most successful second-generation proteins are discovered by a process including trial and error.

10. See ALBERTS ET AL., *supra* note 9, at 104-06.

11. For example, sickle-cell anemia is caused by the mutation of a single nucleotide of the beta-globin gene. LODISH ET AL., *supra* note 9, at 258-59.

12. Ivan Amato, *Chemistry: Changing the Landscape of the Possible*, 262 SCIENCE 507 (1993).

13. See, e.g., PROTEIN ENGINEERING: PRINCIPLES AND PRACTICE (Jeffery L. Cleland & Charles S. Craik eds., 1996); PROTEIN ENGINEERING: A PRACTICAL APPROACH (Anthony R. Rees et al. eds., 1992).

14. ALBERTS ET AL., *supra* note 9, at 174; see also T.J. Graddis & D.L. Oxender, *An Introduction to Protein Engineering*, in CONCEPTS IN PROTEIN ENGINEERING AND DESIGN: AN INTRODUCTION 1, 12 (Paul Wrede & Gisbert Schneider eds., 1994) (stating that information about three-dimensional structure is considered “essential” to predict the effect of a contemplated amino acid substitution).

Despite this limitation, successful muteins have been developed. The first approved pharmaceutical product based on a mutein was Betaseron, a bacterially produced analog of human beta interferon differing from the natural sequence by only a single amino acid.¹⁵ Mutein-based drugs now on the market include Eli Lilly's Humalog (an analog of human insulin), Genentech's TNKase (an analog of human tissue plasminogen activator) and Amgen's Infergen (an analog of human alpha interferon).¹⁶ These pharmaceutical products now aid many thousands of patients each year, and produce annual sales in the hundreds of millions of dollars.

Predictably, owners of patents to the analogous natural-sequence genes or proteins have contended that the high-value mutein-based drugs are covered by their patents. In the first instance, patent-holders have asserted that analogous muteins literally infringe claims of their natural-sequence patents. In the United States, this approach has been a dead end. The Federal Circuit has construed gene or protein claims as limited to the precise sequence or sequences actually described in the patent.¹⁷ Claims that expressly cover variant sequences not disclosed in the specification have generally been found invalid under the enablement and written description requirements.¹⁸ Yet, in *Enzo Biochem, Inc. v. Gen-Probe Inc.*,¹⁹ the Federal Circuit created some uncertainty in this area by remanding for factual

15. The mutein was developed by David Mark, Leo Lin and Shi-Da Yu Lu at Cetus Corporation in the early 1980s. *See* U.S. Patent No. 4,588,585 (issued May 13, 1986). The pharmaceutical product containing this mutein was approved by the Food and Drug Administration (FDA) for the treatment of relapsing-remitting multiple sclerosis in 1993. *See* FDA Press Release, FDA Licenses Interferon Beta-1b (July 23, 1993), *available at* <http://www.fda.gov/bbs/topics/new/new00424.html>. Betaseron is manufactured by Chiron Corporation and sold by Berlex Laboratories.

16. *See* Humalog (Insulin lispro Injection) Prescribing Information (May 1, 2000), *available at* <http://pi.lilly.com/humalog-prescribing.pdf>; TNKase (Tenecteplase) Prescribing Information (June 2000), *available at* <http://www.gene.com/gene/products/information/pdf/tnkase-prescribing.pdf>; Infergen (Interferon alfacon-1) Prescribing Information (Nov. 30, 1998), *available at* <http://208.254.60.143/md/pi/pi.htm>.

17. *See* Schering Corp. v. Amgen Inc., 222 F.3d 1347, 1351-54 (Fed. Cir. 2000); Genentech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555, 1563-65 (Fed. Cir. 1994). European patent law has developed differently. *See* David E. Huizenga, Comment, *Protein Variants: A Study on the Differing Standards for Biotechnology Patents in the United States and Europe*, 13 EMORY INT'L L. REV. 629, 642-54 (1999).

18. *See* Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991).

19. 296 F.3d 1316 (Fed. Cir. 2002).

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determination of whether the written description supported a claim covering specifically disclosed nucleotide sequences as well as mutated variants.²⁰ Nonetheless, it still appears that the principal recourse for the holder of a natural-sequence patent lies in the doctrine of equivalents, which holds that, even if a product does not literally satisfy all the elements of a claim, it may nevertheless infringe the claim if the product practices the claimed invention with only insubstantial variations.²¹

As a result, the doctrine of equivalents takes on special significance for gene and protein patents. That was made clear by the reaction to the Federal Circuit's *Festo* decision, which, until it was reversed by the Supreme Court, limited the number of cases in which the doctrine of equivalents could apply by expanding the scope of prosecution history estoppel.²² In an amicus brief submitted to the Supreme Court urging the importance of the doctrine of equivalents, one biotechnology company declared that "[w]ithout a doctrine of equivalents, a gene patent would be valueless unless it claimed every equivalent sequence of nucleotides."²³ Similarly, Judge Michel warned that the Federal Circuit's *Festo* decision might "drastically limit the scope of protection for biotechnology patents."²⁴ In particular, Judge Michel expressed his concern that, to avoid a protein claim for which the doctrine of equivalents was unavailable, competitors "will only have to substitute at a particular location in the chain an interchangeable amino acid for the particular amino acid recited in the patent claim as occupying that location."²⁵

III. CASE LAW

The doctrine of equivalents is especially important for biotechnology claims because an inventor cannot patent the biological function of a gene or protein based solely on the discovery of a single nucleotide or amino acid sequence with that function. This principle was first developed in cases involving the invalidity defenses of enablement and written descrip-

20. *Id.* at 1327.

21. *See* Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 39-40 (1997); Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 608 (1950).

22. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558 (Fed. Cir. 2000) (en banc), *rev'd*, 535 U.S. 722 (2002).

23. Brief of Amicus Curiae Chiron Corp. in Support of Petitioner at 13, *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002) (No. 00-1543).

24. *Festo*, 234 F.3d at 617 (Michel, J., concurring in part and dissenting in part), *rev'd*, 535 U.S. 722 (2002).

25. *Id.*

tion. In *Amgen, Inc. v. Chugai Pharmaceutical Co.*,²⁶ the Federal Circuit held invalid for lack of enablement a claim to “a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin [EPO] to allow possession of [a particular] biological property.”²⁷ Noting that “the number of claimed DNA encoding sequences that can produce an EPO-like product is potentially enormous,” the court held that Amgen’s disclosure in the patent specification of “[d]etails for preparing only a few EPO analog genes” provided “inadequate support for Amgen’s desire to claim all EPO gene analogs.”²⁸

Similarly, in *Regents of the University of California v. Eli Lilly & Co.*,²⁹ the Federal Circuit held invalid for lack of written description a claim to a nucleotide sequence “having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.”³⁰ The University of California patent claimed all vertebrate insulin genes, even though the specification disclosed only the rat insulin gene. The court held that the specification did not provide an “adequate written description” and observed that a gene patent “requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA.”³¹ Thus, claims to a functionally defined set of genes or proteins, unlimited by the structure of the specific nucleotide or amino acid sequences disclosed, are invalid.

A closely related situation arises when an inventor submits a patent claim covering the particular sequence disclosed in the specification as well as analogs. In *Enzo Biochem, Inc. v. Gen-Probe Inc.*,³² the Enzo patent included a claim to a composition containing any of three nucleotide sequences deposited in a public repository, “discrete nucleotide subsequences thereof,” or “mutated discrete nucleotide sequences” that met a particular hybridization test.³³ The Federal Circuit, on petition for rehearing, held that “reference in the specification to deposits of nucleotide sequences” satisfied the written description requirement, even though the specification did not set forth the actual sequence.³⁴ The court declined,

26. 927 F.2d 1200 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991).

27. *Id.* at 1204 (Claim 7 of U.S. Patent No. 4,703,008 (issued Oct. 27, 1987)).

28. *Id.* at 1213.

29. 119 F.3d 1559 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998).

30. *Id.* at 1563 (Claim 1 of U.S. Patent No. 4,652,525 (issued Mar. 24, 1987)).

31. *Id.* at 1568-69; *accord* *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993).

32. 296 F.3d 1316 (Fed. Cir. 2002).

33. *Id.* at 1326 (Claim 4 of U.S. Patent No. 4,900,659 (issued Feb. 13, 1990)).

34. *Id.* at 1326. The original panel opinion had held to the contrary. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 1013 (Fed. Cir. 2002). For criticism of that opinion, see Harold C. Wegner, *An Enzo White Paper: A New Judicial*

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however, to decide as a matter of law whether the written description supported Enzo's claim, which was directed not only to the deposited sequences, but also to mutations of those sequences. The court "regard[ed] that question as an issue of fact that is best resolved on remand."³⁵

This aspect of *Enzo* may have limited repercussions. The opinion does not ultimately decide the question of written description in that case, and the court expressly noted that the related question of enablement had not been raised by the defendants.³⁶ Moreover, as we discuss in greater detail below, *Enzo* did not involve the relationship between amino acid structure and protein function.³⁷

The leading Federal Circuit case addressing the doctrine of equivalents in connection with a gene or protein patent is *Genentech, Inc. v. Wellcome Foundation Ltd.*³⁸ Genentech sought to enforce its patents on the human tissue plasminogen activator protein (t-PA), and on the gene coding for that protein, against two competitors. A representative claim was to "[a] DNA isolate consisting essentially of a DNA sequence encoding human tissue plasminogen activator."³⁹ Defendant Wellcome made met-t-PA, a product that differed by a single amino acid from native human t-PA, apparently as a result of a cloning error. Defendant Genetics Institute made a product called FE1X, which lacked two of the five domains of the t-PA amino acid sequence and also had two specific amino acid substitutions. The district court construed the claims of the Genentech patents as limited to "the defined human t-PA or a naturally occurring allelic variation of human t-PA" and held that the defendants did not literally infringe.⁴⁰ The case was tried to a jury, which found that both defendants infringed the Genentech patents under the doctrine of equivalents, and the district court denied the defendants' motions for judgment notwithstanding the verdict.⁴¹

On appeal by Genetics Institute (Wellcome dropped its appeal), the Federal Circuit reversed. The court noted that "there are at least four possible definitions set forth in the specification" of the Genentech patents: a

Standard for a Biotechnology "Written Description" Under 35 U.S.C. § 112, ¶ 1, 1 J. MARSHALL REV. INTELL. PROP. L. 254 (2002).

35. *Enzo*, 296 F.3d at 1327.

36. *Id.* at 1327 n.2.

37. *See infra* Part IV.

38. 29 F.3d 1555 (Fed. Cir. 1994).

39. *Id.* at 1558 (Claim 1 of U.S. Patent No. 4,766,075 (issued Aug. 23, 1988)).

40. *Genentech, Inc. v. Wellcome Found. Ltd.*, 14 U.S.P.Q.2d 1363, 1370 (D. Del. Mar. 8, 1990).

41. *See Genentech, Inc. v. Wellcome Found. Ltd.*, 798 F. Supp. 213, 215-16 (D. Del. 1992).

“narrow structural definition” limited to the amino acid sequence of natural t-PA; two “broader structural definition[s]” requiring only particular regions known to be essential for biological activity; and finally a “functional definition” covering any protein with the characteristic biological activity of natural t-PA.⁴² The court decided among these definitions by “avoid[ing] those definitions upon which the PTO could not reasonably have relied when it issued the patent.”⁴³ Consistent with the enablement holding in *Amgen v. Chugai*,⁴⁴ the court held that the broader definitions were not enabled by the specification because those definitions covered “an infinite number of permutations of natural t-PA,” and “[t]here is no basis provided in the specification for determining which of these permutations are operative and which are not.”⁴⁵ Accordingly, the court construed the claim term “human tissue plasminogen activator” to mean “natural t-PA.”⁴⁶

Turning to the doctrine of equivalents, the Federal Circuit ruled that Genetics Institute’s product, FE1X, was not equivalent as a matter of law. In applying the “function, way, result” test, the court acknowledged that it was “confronted with a problem: The issue of whether the ‘way’ or ‘result’ prongs are met is highly dependent on how broadly one defines the ‘function’ of human t-PA.”⁴⁷ If the “function” were defined broadly enough, it would sweep in “any operative variant” of natural t-PA. In light of the specification and the prior art, however, the court ruled that the “function” of natural t-PA included “fibrin binding,” a particular biological activity.⁴⁸ The court decided that the two proteins “possess dramatically different properties and structure,” based on evidence that: (i) the “fibrin binding affinity of FE1X is less than half” that of natural t-PA; (ii) the “mode of binding” is different because FE1X compensates for the deletion of two domains of natural t-PA by a separate amino acid substitution; and (iii) FE1X “behaves significantly differently than human t-PA in the human body,” notably in that it has a half-life about ten times as long.⁴⁹

42. *Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555, 1563-64 (Fed. Cir. 1994).

43. *Id.* at 1564.

44. 927 F.2d 1200, 1213 (Fed. Cir. 1991).

45. *Genentech v. Wellcome*, 29 F.3d at 1564. The court also suggested that the broader definitions might run afoul of the definiteness and written description requirements. *See id.* at 1565 n.25.

46. *Id.* at 1565.

47. *Id.* at 1567.

48. *Id.* at 1567-68.

49. *Id.* at 1568-69.

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In a separate concurring opinion, Judge Lourie stated that he would not have relied on the “function, way, result” test, which he said “fail[s] to fully elucidate the issue, especially when the patented material is a chemical.”⁵⁰ Instead, Judge Lourie would have relied on the facts that FE1X is structurally substantially different from natural t-PA in that it has 15% fewer amino acids, “has ten times the half-life of natural t-PA” and “was not copied, since the accused FE1X is a very different material, independently invented and developed.”⁵¹

Since *Genentech v. Wellcome*, the Federal Circuit has decided only one other case involving whether a mutein infringes a claim to a natural protein. In *Schering Corp. v. Amgen Inc.*,⁵² Schering sought to enforce a patent (issued to Biogen and exclusively licensed to Schering) on a “polypeptide of the IFN- α [alpha interferon] type” against Amgen’s Infergen product, which is a “consensus interferon” with an amino acid sequence that is a rough average of the sequences of all the known alpha interferon sub-types. The district court construed the claim term “a polypeptide of the IFN- α type” as limited to the “single, naturally occurring” protein, “now referred to as IFN- α -1,” described in the specification of Biogen’s patent.⁵³ Schering decided not to proceed under the doctrine of equivalents and consented to having final judgment entered for Amgen.⁵⁴

On appeal, the Federal Circuit affirmed the district court’s claim construction, reasoning that “[b]ecause, at the time of the [patent] application, neither [the inventor] nor others skilled in the art knew of the existence of, let alone the identity of, the specific polypeptides now identified as subtypes of IFN- α , those subtypes cannot be within the scope of the claims.”⁵⁵ Although the doctrine of equivalents was not before the Federal Circuit in *Schering*, the Federal Circuit’s construction of the protein claim as limited to the specific amino acid sequence disclosed in the specification re-affirms the teachings of *Genentech v. Wellcome*.

Thus, the Federal Circuit has not yet held that a gene or protein analog infringes a claim on a specific nucleotide or amino acid sequence. It seems unlikely, however, that this is the final word. No Federal Circuit case has yet confronted an attempt to evade a gene patent with a silent nucleotide substitution. No Federal Circuit case has yet confronted a mutein that has biological properties practically indistinguishable from that of its natural

50. *Id.* at 1570 (Lourie, J., concurring).

51. *Id.*

52. 222 F.3d 1347 (Fed. Cir. 2000).

53. *Schering Corp. v. Amgen Inc.*, 18 F. Supp. 2d 372, 393 (D. Del. 1998).

54. *See Schering Corp. v. Amgen Inc.*, 35 F. Supp. 2d 375 (D. Del. 1999).

55. *Schering*, 222 F.3d at 1353-54.

analog—though it is probable that innumerable such “neutral muteins” could be derived from almost any protein. And of course, between the “practically indistinguishable” and the “dramatically different” lies a continuum of gradations. Almost certainly, courts will be confronted with these harder cases in the coming years.

Three cases that have not reached the Federal Circuit illustrate the range of factual scenarios that will arise. In the recent case, *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*,⁵⁶ the district court held that the accused protein infringed Amgen’s patent under the doctrine of equivalents even though it differed by one amino acid from the claimed sequence. Based on sequencing the human EPO gene, Amgen had obtained a patent on “the 166 amino acid sequence of human EPO shown in Fig. 6,” without realizing that the amino acid at position 166 is cleaved off before the protein is secreted from the cell.⁵⁷ The defendants produced a protein with the identical amino acid sequence for the first 165 positions, but without the amino acid at position 166. The court found that the accused protein “has the same conformational structure and biological activity” as the claimed protein.⁵⁸ Although the defendants argued in the abstract that “a change in even just one amino acid can have a significant effect on the clinical function of a protein,” they introduced no evidence that the amino acid at position 166 of human EPO had such an effect.⁵⁹ The court therefore held that the accused protein infringed under the doctrine of equivalents.⁶⁰

56. 126 F. Supp. 2d 69 (D. Mass. 2001), *appeal pending*, No. 01-1191 (Fed. Cir.). This case, generally known as *Amgen v. TKT*, has attracted considerable public interest. *See, e.g.*, Andrew Pollack, *Two Paths to the Same Protein*, N.Y. TIMES, Mar. 28, 2000, at C1.

57. *Amgen*, 126 F. Supp. 2d at 86.

58. *Id.* at 133.

59. *Id.* at 134.

60. The earlier case of *Hormone Research Foundation, Inc. v. Genentech, Inc.*, 708 F. Supp. 1096 (N.D. Cal. 1988), presented a related and interesting situation. As a result of sequencing errors in the course of an effort to sequence natural human growth hormone (“HGH”), a patent was obtained which literally recited the sequence of a mutein varying by four amino acids from natural HGH. This patent was asserted against Genentech’s natural-sequence HGH product. The Federal Circuit rejected the argument that the claims should be construed to literally cover proteins with a sequence “similar” to that disclosed in the specification, but did so for reasons particular to the details of the prosecution history of the Hormone Research Foundation patent. *Hormone Research Foundation, Inc. v. Genentech, Inc.*, 904 F.2d 1558 (Fed. Cir. 1990). The court remanded for trial on the issue of infringement under the doctrine of equivalents, and the case was subsequently settled.

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A similar case is reportedly pending in the Patents Court in England, involving a U.S. patent. As described in an amicus brief submitted to the Supreme Court in *Festo*,⁶¹ the licensee of an antibody protein patent (covering a sequence of 1320 amino acids) altered a single amino acid, allegedly with “no significant impact” on the protein’s biological activity, and then asserted noninfringement and refused to pay royalties. This case highlights the potential for copyists to make amino acid substitutions solely to try to evade a patent on the natural sequence.

A fact situation with both important similarities and important differences was presented by *Hoffmann-La Roche Inc. v. Berlex Laboratories, Inc.*,⁶² a case taken into private arbitration and settled without published opinion.⁶³ Roche sought to enforce a patent (issued to Genentech) on a composition claiming “a nonglycosylated polypeptide having the amino acid sequence of a mature human [beta] interferon.”⁶⁴ The specification, and some of the claims, recited that 166-amino-acid sequence. Berlex sells a pharmaceutical product containing a beta interferon mutein, in which one of the 166 amino acids (the cysteine at position 17) is replaced by a different amino acid (a serine).⁶⁵ Roche claimed first that its patent should be construed to literally cover analog sequences in addition to the naturally occurring amino acid sequence, which would have meant that Berlex’s mutein literally infringed. Berlex rejoined that the patent specification did not provide a written description of the innumerable potential analogs, nor did it enable a person skilled in the art to make a functional analog protein. The claim would therefore be invalid if it were that broad, and should instead be construed narrowly.

Roche further asserted that, even if the claim were construed as limited to the naturally occurring sequence, Berlex’s mutein infringed under the doctrine of equivalents. Roche argued that the mutein was equivalent to the claimed protein because both exhibited anti-viral activity, the essential biological function of human beta interferon. Berlex countered that its mutein had properties substantially improved over those of the claimed protein. This contention was based on research showing that the amino

61. Brief of Amicus Curiae Celltech Group PLC in Support of Petitioner at 6, *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002) (No. 00-1543).

62. No. 96-3554 (D.N.J. filed July 25, 1996).

63. The authors, together with lead counsel Richard W. Clary, a partner of Cravath, Swaine & Moore, represented Berlex. The outcome of the arbitration is confidential.

64. U.S. Patent No. 5,460,811 (issued Oct. 24, 1995), Claim 1. The claim refers to “fibroblast interferon,” now known as beta interferon.

65. This is the Betaseron product. See *supra* note 15.

acid substitution led to higher specific activity and greater stability, as compared to the claimed protein.⁶⁶ Berlex maintained that the improved properties of the mutein rendered it nonequivalent to the claimed protein.

IV. LITERAL COVERAGE OF UNTRIED SECOND-GENERATION GENES AND PROTEINS

There are two ways in which the holder of a patent on a naturally occurring gene or protein may argue that an engineered analog sequence infringes the patent literally. In Part IV.A, we discuss the construction of claims directed to protein function, and defend the Federal Circuit's holding that such claims are limited to the sequence described in the specification. In Part IV.B, we discuss the validity of claims expressly directed to variant sequences not described in the specification, and argue that claims involving prediction as to the functionality of the resulting mutein will usually be invalid.

A. The Construction of Claims Directed to Protein Function

The lesson from both *Genentech v. Wellcome* and *Schering* is that claims to a gene or protein, referred to by common name or function (such as “a DNA sequence encoding human tissue plasminogen activator” or “a polypeptide of the IFN- α type”) rather than by sequence, will be construed as limited to the specific nucleotide or amino acid sequences disclosed in the specification.⁶⁷ This result is predicated on the lack of enablement for variant nucleotide or amino acid sequences that the inventor has not made or tested.⁶⁸

66. See David F. Mark et al., *Site-Specific Mutagenesis of the Human Fibroblast Interferon Gene*, 81 PROC. NAT'L ACAD. SCI. USA 5662 (1984). The claimed protein is non-glycosylated (*i.e.*, it lacks certain sugar side chains usually occurring on the naturally produced protein), and as a result does not exhibit the specific activity and stability of the natural (and glycosylated) human beta interferon protein as expressed in the human body. Apparently, in solution improper chemical bonds (“disulfide bonds”) form between the non-glycosylated beta interferon protein molecules, causing the molecules to clump together and lose much of their bioactivity. The creators of Berlex's mutein solved this problem by replacing one of three cysteines in the natural amino acid sequence, a substitution which largely eliminated the formation of improper disulfide bonds. See *id.* at 5665-66.

67. See *Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1351-54 (Fed. Cir. 2000); *Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555, 1563-65 (Fed. Cir. 1994).

68. Thus, we see no need in this context to reach the interesting questions regarding the scope of the written description doctrine disputed by some judges on the Federal Circuit in *Enzo*. See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 42 Fed.

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That is a sound rule.⁶⁹ An inventor should not be entitled to a patent literally covering nucleotide or amino acid sequences not specifically described in the specification. Given the *a priori* unpredictability of the properties of novel proteins, claims to all sequences with a particular biological activity are not sufficiently described or enabled. For a medium-length protein, thousands of unique variants can be created, each differing from the natural sequence by only a single amino acid. Allowing just two amino acid substitutions already yields millions of alternative sequences.⁷⁰ Many of these variant proteins will be functionally indistinguishable from the natural-sequence protein, and most of the rest will be biologically inactive or unacceptable for clinical use due to side effects such as immunogenicity. But, in a few cases, currently unpredictable in advance, the amino acid substitution may result in an improvement. The astronomical number of potential combinations, however, means that disclosure of the natural sequence does not meaningfully enable the reader to identify or make any of those potential improved molecules. This counsels against permitting claims to a functionally defined set of genes or proteins.

A contrary rule would stifle innovation. A gene or protein patent with functional coverage would discourage others from seeking alternative natural or synthetic sequences with the same basic biological activity but improved properties. At the same time, the holder of a gene or protein patent has little incentive to develop an improved version of that gene or protein. Thus, if gene and protein patents dominated all variant nucleotide or amino acid sequences, no one would have an economic incentive to experiment with variants, and protein engineering would be forestalled for the length of the patent term.⁷¹

In theory the “reverse doctrine of equivalents” could provide some relief. For example, in *Scripps Clinic & Research Foundation v. Genentech*,

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- Appx. 439, 440 (Fed. Cir. 2002) (Lourie, J., concurring in denial of rehearing en banc); *id.* at 445 (Rader, J., dissenting from denial of rehearing en banc).
69. For criticism of the Federal Circuit’s case law in this area, see Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 BERKELEY TECH. L.J. 615, 639-99 (1998); Harris A. Pitlick, *The Mutation of the Description Requirement Gene*, 80 J. PAT. & TRADEMARK OFF. SOC’Y 209 (1998).
70. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).
71. We disagree with a commentator who argues that the incentive to invent “has little to offer” regarding “whether a patent on a recombinant protein should protect variations and improvements of that protein.” Yusing Ko, Note, *An Economic Analysis of Biotechnology Patent Protection*, 102 YALE L.J. 777, 795 (1992).

Inc.,⁷² the Federal Circuit held that defendant Genentech was entitled to a trial on whether its recombinant human Factor VIII:C, although literally covered by Scripps' patent on human Factor VIII:C, was so different in purity and specific activity that it avoided infringement under the "reverse doctrine of equivalents."⁷³ The doctrine, however, has so rarely been successfully invoked that it cannot provide enough comfort to justify major investment. Moreover, a defendant who invokes this doctrine would still face the burden of proving lack of infringement.⁷⁴

Alternatively, one critic of the Federal Circuit's case law on enablement has proposed that a patentee be permitted "to claim all of the modifications that code for proteins with similar biological activity and that are substantially homologous to the native protein,"⁷⁵ except for "protein modifications which may be similar in structure yet superior in biological activity."⁷⁶ While we are sympathetic to this author's goal, his proposal does not accord with the law on enablement. The specification of a typical patent claiming a naturally occurring protein does not enable the creation of muteins with equivalent biological activity any more than it enables the creation of muteins with superior biological activity. Instead of tampering with the doctrine of enablement, we suggest that the best way to strike the necessary balance for gene and protein inventions is to limit the claims to a narrow literal claim scope but use the doctrine of equivalents to prevent infringers from avoiding the patents through insubstantial changes, as we discuss later.⁷⁷

B. The Validity of Claims Directed to Variant Nucleotide or Amino Acid Sequences

A more difficult question is whether patent applicants can broaden the literal scope of their patent coverage by claiming variant nucleotide or

72. 927 F.2d 1565 (Fed. Cir. 1991).

73. *Id.* at 1581.

74. See 5A DONALD S. CHISUM, PATENTS § 18.04[4], at 18-392; § 18.04[4][d], at 18-400 (1998).

75. Kenneth G. Chahine, *Enabling DNA and Protein Composition Claims: Why Claiming Biological Equivalents Encourages Innovation*, 25 AIPLA Q.J. 333, 368 (1997).

76. *Id.* at 337.

77. Some commentators have criticized the Federal Circuit's case law on obviousness and enablement for making it relatively easy to obtain a gene or protein patent, but rendering those patents "extremely narrow, at least in literal scope." Dan L. Burk & Mark A. Lemley, *Biotechnology's Uncertainty Principle* 29 (Mar. 18, 2002 working paper), available at <http://papers.ssrn.com>. We agree with the premise, but believe that the doctrine of equivalents can solve the problem of claim scope.

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amino acid sequences that the applicants have neither made nor tested.⁷⁸ A common approach for gene claims is to claim all nucleotide sequences that hybridize to the defined sequence.⁷⁹ That is the type of claim at issue in *Enzo*, where the claim encompassed the specifically disclosed sequences and “mutated” sequences within a particular “hybridization ratio.”⁸⁰ Unfortunately, the *Enzo* court did not attempt to reconcile its disposition of the written description challenge to a hybridization-type gene claim with Federal Circuit case law invalidating gene or protein claims based on protein function.⁸¹

We suggest that the key to understanding this aspect of *Enzo* is that nucleic acid hybridization is much better understood than the structure/function relationship for proteins. The claims in *Enzo* were to a genetic probe and not, as in *Amgen* and *Eli Lilly*, a nucleotide sequence encoding a functional protein. The effects of changes in the nucleotide sequence on nucleic acid hybridization are easy to predict.⁸² Thus, a specification can describe and enable hybridizing variants to a specifically disclosed nucleotide sequence. By contrast, scientists cannot predict *a priori* how a change in amino acid sequence will affect the function of the resulting protein.

More problematic than the claims in *Enzo*, then, are claims directed to variant amino acid sequences, or variant nucleotide sequences that code for proteins that retain the function of the native protein. The Patent Office has rejected claims to variant sequences that retain biological activity, when the specification provides no guidance as to the effect of particular nucleotide or amino acid substitutions.⁸³ In some cases, however, the Patent Office has approved claims covering variant sequences when the specification provided guidance as to what types of modifications fall

78. See Stephen G. Whiteside, Note, *Patents Claiming Genetically Engineered Inventions: A Few Thoughts on Obtaining Broad Property Rights*, 30 NEW ENG. L. REV. 1019, 1059-64 (1996).

79. See Mark J. Stewart, Note, *The Written Description Requirement of 35 U.S.C. § 112(1): The Standard After Regents of the University of California v. Eli Lilly & Co.*, 32 IND. L. REV. 537, 559-60 (1999).

80. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1322 (Fed. Cir. 2002). (Claim 4).

81. See *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200 (Fed. Cir. 1991).

82. For discussion of nucleic acid hybridization, see ALBERTS ET AL., *supra* note 9, at 300-07.

83. See *Ex parte Maizel*, 27 U.S.P.Q.2d 1662, 1664-65 (Bd. Pat. App. & Interf. Apr. 23, 1993); *Ex parte Hudson*, 18 U.S.P.Q.2d 1322, 1323 (Bd. Pat. App. & Interf. Dec. 21, 1990).

within the claim scope. For instance, a number of patents have issued with claims to a specified amino acid sequence along with any variant sequence involving a “conservative amino acid substitution.” The specification of such patents typically includes boilerplate guidance on how to make variant proteins, often with a listing of “exemplary substitutions” for each of the twenty amino acids.⁸⁴

In the absence of any case law, this type of expansive claim drafting is no doubt prudent. Yet patent-holders should not be able to circumvent the sound rule of *Genentech v. Wellcome* and *Schering* merely by referring to the possibility of making variant proteins. Indeed, it is doubtful that claims of this sort could hold up under scrutiny for written description and enablement.⁸⁵ For persons skilled in the art, it generally remains unpredictable what effect even so-called “conservative amino acid substitutions” would have on a protein’s biological activity.⁸⁶ Indeed, claims of this type appear to be inconsistent with the Patent Office’s new Written Description Guidelines, which permit claims to “functional characteristics when coupled with a *known or disclosed correlation between function and structure*.”⁸⁷ The Federal Circuit relied upon this statement from the Guidelines in *Enzo*.⁸⁸

To be sure, if science makes it possible to predict—with reasonable certainty—the effect of specific amino acid substitutions on the biological activity or other important properties of proteins, there could be an expansion of what may fairly be claimed beyond sequences actually made and

84. See, e.g., U.S. Patent No. 5,864,020, Claim 1 (issued Jan. 26, 1999) (claiming the specified amino acid sequences for mature murine and human hepatoma transmembrane kinase receptor (Htk) ligands, as well as the naturally occurring amino acid sequence for mature Htk ligand from [any other] animal species; “allelic variants of [those] sequences”; and sequences “having a single preferred conservative amino acid substitution as defined in Table 1”).

85. See *Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997); *Chugai Pharm.*, 927 F.2d at 1212-13.

86. See MANUAL OF PATENT EXAMINING PROCEDURE § 2144.08, at 2100-141 (8th ed. 2001) (“The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position.”); see also *supra* note 14 and accompanying text.

87. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, “Written Description” Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001) (emphasis added).

88. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002).

tested.⁸⁹ The predictability of the art is an important factor in the enablement analysis.⁹⁰ For now, though, claims to protein analogs that the inventor did not actually make and test should generally be held invalid.

Two exceptions to this general rule come to mind. First, some proteins are already well characterized, and their three-dimensional structure determined, such that scientists know to a reasonable certainty which amino acids are essential for biological activity, and which are inessential. Over time, more proteins will fall into this category.⁹¹ In such cases it may well be possible to appropriately describe, enable and claim various families of analog molecules. Second, the general rule should not apply if the inventor has made and tested analogs structurally related to those he claims. In such cases, the trial and error of making muteins has elucidated a principle of amino acid substitution that allows the inventor to claim an appropriately defined genus of muteins encompassing ones he never actually made.⁹²

V. THE APPLICATION OF THE DOCTRINE OF EQUIVALENTS TO SECOND-GENERATION GENES AND PROTEINS

Given the limited ability to obtain a patent that literally reads on variant sequences, the patent-holder who seeks to enforce a gene or protein patent against a variant sequence likely must rely on the doctrine of equivalents. The critical question, then, is how “equivalence” should be determined for such patents. In Part V.A, we review various problems with the existing case law on the doctrine of equivalents when applied to gene or protein patents. In Part V.B, we suggest that the “known interchangeability” test for equivalence is the best way to resolve infringement claims involving second-generation genes and proteins.

89. *See Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374 n.10 (Fed. Cir. 1999) (“In view of the rapid advances in science, we recognize that what may be unpredictable at one point in time may become predictable at a later time.”).

90. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). For discussion of the importance of the perception of biotechnology as an “unpredictable art,” see Stewart, *supra* note 77, at 556-58.

91. *See Chahine, supra* note 74, at 359-60.

92. *See Ex parte Mark*, 12 U.S.P.Q.2d 1904, 1905-07 (Bd. Pat. App. & Interf. 1989) (upholding claims to any human beta interferon mutein “having at least one of [its three] cysteine residues substituted by another amino acid and said mutein exhibiting the biological activity of said native protein,” based on a disclosure of the structural significance of cysteines to the particular protein and the inventors’ creation and testing of certain cysteine-depleted muteins); *cf. In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996) (remanding to the Board of Patent Appeals and Interferences on adequacy of written description for human gamma interferon mutein).

A. Problems with the Doctrine of Equivalents

1. *The All-Elements Rule Should Apply to the Sequence as a Whole*

We should note at the outset a potential pitfall in applying the doctrine of equivalents to gene or protein patents. Under the “all elements” rule as taught by the Supreme Court in *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*,⁹³ “[e]ach element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole.”⁹⁴ Accordingly, some commentators suggest that each nucleotide in a gene patent and each amino acid in a protein patent may constitute a separate claim element.⁹⁵ But most amino acids in any particular protein do not perform a known function of their own; rather, the amino acid sequence as a whole determines the protein’s three-dimensional structure, which in turn is essential to its function. Thus, it makes no sense to consider each amino acid to be a separate claim element.

Moreover, to do so would lead to absurd results. For example, the holder of a protein patent could get to the trier of fact on an equivalence claim against a variant protein in which one amino acid had been substituted for another, but the same patent-holder would lose as a matter of law if the variant protein had instead been made by leaving out one amino acid altogether. For example, in *Amgen v. TKT*, where the defendants omitted the amino acid in the 166th and final position without affecting the protein’s properties,⁹⁶ the doctrine of equivalents would be unavailable if that single amino acid were considered a “claim element” in its own right. Thus, in a gene or protein patent, the entire sequence should be considered a single element.

93. 520 U.S. 17 (1997).

94. *Id.* at 29.

95. See Lawrence S. Graham, Note, *Equitable Equivalents: Biotechnology and the Doctrine of Equivalents After Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 6 J.L. & POL’Y 741, 783 (1998); Robert D. Bajefsky & Howard W. Levine, *Impact of ‘Hilton Davis’ on Biotech Is Unclear*, NAT’L L.J., June 16, 1997, at C9.

96. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 133 (D. Mass. 2001), *appeal pending*, No. 01-1191 (Fed. Cir.).

2. *The Function-Way-Result Test Produces Arbitrary and Unpredictable Results*

The leading test for equivalence—and the test applied by the Federal Circuit in *Genentech v. Wellcome*—is the function-way-result test.⁹⁷ However, this three-part analysis is highly indeterminate, and is particularly unsuited for measuring the scope of equivalence for biotechnology patents.

The question of equivalence under the function-way-result test often depends entirely on how the “function” of the patented gene or protein is characterized. For example, in *Genentech v. Wellcome*, the Federal Circuit reversed the district court on equivalence because the Federal Circuit chose a narrower definition of the “function” of human t-PA.⁹⁸ Many gene and protein patents will raise the same issue: the more specific the articulation of the patented gene’s or protein’s “function,” the less likely the variant gene or protein will be found to have the same “function.”⁹⁹ In other words, the outcome of the three-part analysis will often depend entirely on the first step, namely which of the different “functions” proffered by the parties the court decides to accept. Thus, the outcome of function-way-result analysis in this context is highly manipulable and unpredictable.

The Federal Circuit has attempted to add some certainty to the selection of the “function” of a claim limitation by instructing courts to look at “the intended function as seen in the context of the patent, the prosecution history, and the prior art.”¹⁰⁰ In many likely future cases involving gene and protein patents, however, these sources will refer both to broader and narrower “functions,” and the court’s selection of one of these “functions” for purposes of equivalence analysis will remain troublingly arbitrary.

Moreover, basing the “function” on the patent specification and the prior art raises a problem of timing. The Supreme Court held in *Hilton Davis*¹⁰¹ that equivalence is determined at the time of infringement.¹⁰² If the “function” for purposes of equivalence analysis is based on what was known to a person skilled in the art at the time of invention, then any properties of the patented gene or protein discovered between the time of

97. *See* *Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555, 1567 (Fed. Cir. 1994).

98. *See id.*

99. *See* 5A CHISUM, *supra* note 73, § 18.04[5], at 18-407.

100. *Genentech*, 29 F.3d at 1567; *see also* *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1425 (Fed. Cir. 1994).

101. 520 U.S. 17 (1997).

102. *Id.* at 37.

invention and the time of infringement would have to be disregarded. Even more important, any new properties of the variant gene or protein would be irrelevant to the equivalence analysis. Thus, a protein analog with a significant new property not shared by the patented protein would infringe, whereas another protein analog with no new properties but a substantial difference in the existing property of the patented protein would not. That outcome is inconsistent with the Supreme Court's decision in *Hilton Davis* that equivalence is determined at the time of infringement.¹⁰³

Additionally, the function-way-result analysis is particularly problematic in biotechnology cases because the "way" component frequently collapses into the "result" component. Scientific understanding of the way proteins act at the molecular level is not yet well developed. As the Federal Circuit cautioned in *Genentech v. Wellcome*, "[w]e are mindful that the state of science in this area of endeavor is very imprecise."¹⁰⁴ Consequently, even if a protein analog exhibits very different "results" from the natural protein, scientists may not know the "way" in which the differences arise. Thus, in many biotechnology cases the "way" prong will be meaningless. The Supreme Court's observation in *Hilton Davis* that the function-way-result test is more "suitable for analyzing mechanical devices" than it is for analyzing "other products or processes" has particular application to biotechnology cases.¹⁰⁵

3. A "Hypothetical Claim" Analysis Is Unduly Restrictive

Another mode of analyzing equivalence that the Federal Circuit sometimes uses is "hypothetical claim" analysis. This approach is based on the premise that a patent-holder should not be permitted to use the doctrine of equivalents to obtain coverage for which the PTO would not have awarded literal claims in light of the prior art. Accordingly, the Federal Circuit has suggested that "it may be helpful to conceptualize the limitation on the scope of equivalents by visualizing a *hypothetical* patent claim, sufficient in scope to *literally* cover the accused product. The pertinent question then

103. In a sense, this issue is the flip side of the issue in *Hilton Davis*. In that case, the Supreme Court held that "after-arising equivalents" could still infringe. *Id.* at 37. Here, the issue is whether later-arising nonequivalence can lead to a finding of noninfringement.

104. *Genentech v. Wellcome*, 29 F.3d at 1569.

105. *Hilton Davis*, 520 U.S. at 39-40; *see also Genentech*, 29 F.3d at 1570 (Lourie, J., concurring).

becomes whether that hypothetical claim could have been allowed by the PTO over the prior art.”¹⁰⁶

At least in the case of patents on natural gene or protein sequences, “hypothetical claim” analysis usually does not bar the assertion of equivalence against a variant sequence with the same biological properties. If the inventor was the first to isolate the natural protein, a hypothetical claim to a protein with the particular biological properties characteristic of that protein would not be anticipated or rendered obvious by the prior art, and therefore could have been allowed.

Several commentators, however, have proposed for gene and protein patents an “expanded hypothetical claim analysis” that would ask not just whether the hypothetical claim reads on the prior art, but also whether the specification enabled the full scope of such a claim.¹⁰⁷ That proposal should not be adopted. The Federal Circuit has already held in *Genentech v. Wellcome* that protein claims reaching beyond specifically recited sequences would be invalid for lack of enablement because the effects of untried sequence variations are inherently unpredictable.¹⁰⁸ Thus, requiring full enablement of the hypothetical claim (as of the time of the application) would bar application of the doctrine of equivalents to any variant sequence not specifically described in the specification. Under this test, even an amino acid substitution with absolutely no effect on biological properties of the protein—made for the sole purpose of evading a patent on the natural sequence—would escape infringement. That result cannot be justified.

4. *The Separate Patentability of the Accused Sequence Should Not Be Determinative*

Finally, as part of a doctrine of equivalents inquiry, courts often look to whether the accused product is separately patentable. The Federal Circuit has held that a finding by the PTO that the accused product is separately patentable due to improved properties is evidence that it is not

106. *Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 684 (Fed. Cir.) (emphasis in original), *cert. denied*, 498 U.S. 922 (1990); *see also* *K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1367-68 (Fed. Cir. 1999).

107. *See* Laura A. Handley, *Refining the Graver Tank Analysis with Hypothetical Claims: A Biotechnology Exemplar*, 5 HARV. J.L. & TECH. 31 (1991); Michael T. Siekman, *The Expanded Hypothetical Claim Test: A Better Test for Infringement for Biotechnology Patents Under the Doctrine of Equivalents*, 2 B.U. J. SCI. & TECH. L. 6 ¶¶ 17, 22, 39, 46 (1996). To date, no court has required the “hypothetical claim” to meet written description or enablement requirements. *See* 5A CHISUM, *supra* note 73, § 18.04[2][d][ii][D], at 18-376.

108. 29 F.3d at 1564-65.

equivalent to the claimed product: the same unexpected advantages that render the accused product nonobvious over the prior art also render it nonequivalent.¹⁰⁹ On the other hand, the Federal Circuit has insisted that “separate patentability does not avoid equivalency as a matter of law.”¹¹⁰ The court has reasoned that, “where defendant has appropriated the material features of the patent in suit, infringement will be found even when those features have been supplemented and modified to such an extent that the defendant may be entitled to a patent for the improvement.”¹¹¹

Despite the Federal Circuit’s caveat, some commentators have urged that separate patentability, and in particular whether a variant nucleotide or amino acid sequence would be obvious over the claimed gene or protein, should determine infringement under the doctrine of equivalents.¹¹² This, however, would unduly restrict the scope of patents on natural sequences because it is relatively easy to obtain a patent on a novel nucleotide or amino acid sequence.

Although “structural similarity between claimed and prior art subject matter . . . creates a *prima facie* case of obviousness,” that presumption may be rebutted by “data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have.”¹¹³ If the applicant for a patent on a variant sequence cannot point to *any* novel or improved property or provide a reason why the results of a particular amino acid substitution would be unexpected, the application may be denied for obviousness. For example, in *Ex parte Anderson*,¹¹⁴

109. *See* *Zygo Corp. v. Wyko Corp.*, 79 F.3d 1563, 1570 (Fed. Cir. 1996); *National Presto Indus., Inc. v. West Bend Co.*, 76 F.3d 1185, 1191-92 (Fed. Cir. 1996); *Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948, 954 & n.28 (Fed. Cir. 1993).

110. *Fiskars, Inc. v. Hunt Mfg. Co.*, 221 F.3d 1318, 1324 (Fed. Cir. 2000); *see also* *Hoechst Celanese Corp. v. BP Chem. Ltd.*, 78 F.3d 1575, 1582 (Fed. Cir. 1996).

111. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1580 (Fed. Cir. 1984) (citing *Bendix Corp. v. United States*, 600 F.2d 1364 (Ct. Ce. 1979)).

112. *See* Qing Lin, Note, *A Proposed Test for Applying the Doctrine of Equivalents to Biotechnology Inventions: The Nonobviousness Test*, 74 WASH. L. REV. 885 (1999); *see also* Siekman, *supra* note 105 ¶¶ 9-14; Sean Johnston, Comment, *Patent Protection for the Protein Products of Recombinant DNA*, 4 HIGH TECH. L.J. 249, 273 (1990).

113. *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990) (en banc), *cert. denied*, 500 U.S. 904 (1991); *see also* MANUAL OF PATENT EXAMINING PROCEDURE § 2144.09 (8th ed. 2001). *Dillon* involved a chemical compound. For an argument that the “structural similarity” holding of *Dillon* should not apply to proteins and their analogs, which are typically much more complex, *see* KENNETH J. BURCHFIEL, BIOTECHNOLOGY AND THE FEDERAL CIRCUIT § 6.9, at 110-18 (1995).

114. 30 U.S.P.Q.2d 1866 (Bd. Pat. App. & Interf. Mar. 14, 1994).

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where the applicants isolated a naturally occurring allele coding for a protein differing by one amino acid from the protein encoded by the nucleotide sequence in the prior art, the Board of Patent Appeals and Interferences denied the application. The Board stated that “it is well known in the art that usually the substitution of one amino acid for another in a nonessential region of the protein will have no effect on the biological activity of the protein.”¹¹⁵ But in most instances it will not be difficult to overcome a *prima facie* obviousness rejection by identifying a property—perhaps irrelevant to the intended use of the claimed protein—in which the two sequences differ, or by arguing that the results of a particular amino acid substitution were unexpected. It is “hard to make arguments of nonobviousness stick with regard to biotechnological invention.”¹¹⁶

A further problem with an obviousness test for equivalence is one of timing. Equivalence is measured at the time of infringement,¹¹⁷ whereas obviousness is evaluated retroactively at “the time the invention was made.”¹¹⁸ Thus, an infringer who makes a protein with a minor variant that at the time of infringement was known to be equivalent could escape liability so long as the effect of his amino acid substitution was not obvious at the time the natural sequence was discovered—perhaps many years earlier. Alternatively, a person skilled in the art might wrongly believe at the time of the invention that a novel protein had improved properties, but might realize by the time of infringement that it was equivalent to the natural analog after all. In either of these situations, the mutein should infringe under the doctrine of equivalents because the mutein offers no improvement over the claimed protein at the time of infringement and would be used only to evade the patent. The proposed obviousness test would only lead the fact-finder astray.

115. *Id.* at 1869; see also *In re Mayne*, 104 F.3d 1339, 1343-44 (Fed. Cir. 1997) (affirming a rejection on obviousness grounds where the applicant failed to carry his burden to show that a fusion protein had any unexpected properties); *Ex parte Gray*, 10 U.S.P.Q.2d 1922, 1926 (Bd. Pat. App. & Interf. Mar. 14, 1989) (holding that a recombinant human protein with an additional methionine residue as a result of bacterial expression was obvious in light of the native human protein).

116. John M. Golden, *Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System*, 50 EMORY L.J. 101, 129-30 (2001). For a helpful analysis of the case law on the obviousness of variant genes or proteins, see Philippe Ducor, *Recombinant Products and Nonobviousness: A Typology*, 13 SANTA CLARA COMPUTER & HIGH TECH. L.J. 1, 48-56 (1997).

117. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 37 (1997).

118. 35 U.S.C. § 103 (2000).

Separate patentability of the variant gene or protein should not therefore be determinative of infringement under the doctrine of equivalents. A PTO finding of nonobviousness is relevant, but not dispositive of equivalence.

B. The Known Interchangeability Test for the Doctrine of Equivalents

In contrast to the unsuccessful approaches reviewed above, we suggest that the “known interchangeability” test, a well established strand of the case law on the doctrine of equivalents, is a promising methodology for evaluating equivalence to a gene or protein patent.

In *Graver Tank & Manufacturing Co. v. Linde Air Products Co.*,¹¹⁹ the Supreme Court held that “[a]n important factor” in the doctrine of equivalents “is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was.”¹²⁰ More recently, the Federal Circuit in *Hilton Davis* held that the “function, way, result” test was not “‘the’ test for equivalency,” and emphasized that other factors should also be considered when appropriate. One of the factors identified by the Federal Circuit as “important” was whether a person skilled in the art “would have known of the interchangeability” of the accused element with the patented element.¹²¹

The advantage of the known interchangeability test is that it properly focuses on the functional differences between the two genes or proteins. Two nucleotide or amino acid sequences are interchangeable if a person skilled in the art would be relatively indifferent as to which one was used. That is, if a person skilled in the art would have a marked preference for one sequence over the other, then the sequences are not equivalent even though one sequence may to some extent or under some circumstances be useable in place of the other. Known interchangeability is thus an *objective* measure of whether there is a substantial difference between the accused gene or protein and the patented one.

Objective factors are well suited for the finder of fact in patent cases. The Supreme Court has described known interchangeability as “one of the express objective factors noted by *Graver Tank* as bearing upon whether the accused device is substantially the same as the patented invention.”¹²² As an objective measure of equivalency, known interchangeability is

119. 339 U.S. 605 (1950).

120. *Id.* at 609.

121. *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1518-19 (Fed. Cir. 1995) (en banc), *rev'd on other grounds*, 520 U.S. 17 (1997).

122. *Hilton Davis*, 520 U.S. at 36.

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analogous to the “secondary considerations” of nonobviousness,¹²³ which are examined in light of the “real world facts.”¹²⁴ In the obviousness context, the Federal Circuit has declared that “[t]he significance of a new structure is often better measured in the marketplace than in the courtroom.”¹²⁵ So, too, with the doctrine of equivalents for gene or protein patents: whether a variant nucleotide or amino acid sequence is substantially improved over the claimed gene or protein will often be reflected in the variant sequence’s success, or lack thereof, in the marketplace.

Knowledge of the interchangeability of the two sequences can come either from the prior art or from the work of the creator of the second sequence. Because the results of protein engineering are so unpredictable, there often will be no data on whether the accused sequence is interchangeable with the patented one until the work of the creator of the accused sequence. Permitting a finding of interchangeability based on the very work leading to the accused sequence is consistent with the determination of equivalence at the time of infringement¹²⁶ and is necessary to prevent easy evasion of a gene or protein patent through creation of a “neutral mutin.”¹²⁷

Some cases will be easy to decide using the known interchangeability test. A sequence with a “silent” nucleotide substitution (*i.e.*, one that produces no alteration in the amino acid sequence of the expressed protein) will always infringe a patent on the original gene under the doctrine of equivalents. A sequence with an amino acid substitution that has no perceptible effect on biological activity will likewise infringe a patent on the original protein.¹²⁸

123. *Graham v. John Deere Co.*, 338 U.S. 1, 17-18 (1966).

124. *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546 (Fed. Cir. 1984).

125. *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991).

126. *See Hilton Davis*, 520 U.S. at 37 (holding that the proper time to determine equivalence is at the time of infringement).

127. *See generally* Martin J. Adelman & Gary L. Francione, *The Doctrine of Equivalents in Patent Law: Questions That Pennwalt Did Not Answer*, 137 U. PA. L. REV. 673, 728 (1989) (arguing that “the sole legitimate function of the doctrine” of equivalents is to “ensure[] that patent protection is not eviscerated by technology developed after the patent issues”).

128. *See* Jeffrey P. Kushan, Comment, *Protein Patents and the Doctrine of Equivalents: Limits on the Expansion of Patent Rights*, 6 HIGH TECH. L.J. 109, 113 (1991) (“[F]ew would hesitate to label a ‘conservative’ amino acid substitution in a polypeptide sequence of a complex, patented protein, which was implemented for the sole purpose of escaping the literal scope of a patent claim, as

Conversely, a variant sequence with substantially improved biological activity would likely not be considered by a person skilled in the art to be interchangeable with the original sequence, and would not infringe. Presumably, the reason that Schering did not pursue infringement under the doctrine of equivalents in its case is that Amgen's "consensus interferon" has substantially higher anti-viral activity than the specific IFN- α -1 protein that the court found was covered by the patent claim.¹²⁹

A variant nucleotide or amino acid sequence with an entirely new, and useful, property would likewise not be interchangeable with the original sequence—even if the two sequences were indistinguishable with respect to the properties of the original sequence—and would therefore not infringe.¹³⁰ There should not be a limit on the type of property that can serve to distinguish two sequences: proteins can differ not only in biological activities, but also in their stability, ease of purification, or other characteristics that may make one sequence a preferred pharmaceutical agent.

The known interchangeability test would decide *Genentech v. Wellcome* the same way as the Federal Circuit did, but with less difficulty. Genentech's claimed human t-PA is used in thrombolytic therapy (*i.e.*, to break down blood clots) for victims of heart attacks. The evidence was that the accused variant protein (FE1X) has a substantially longer half-life, "thereby eliminating the need for continuous infusion of t-PA product."¹³¹ Although the FE1X variant itself apparently has never been approved in the United States, in the wake of *Genentech v. Wellcome* other drugs con-

anything but an 'unimportant and insubstantial' modification." (footnotes and citations omitted)).

129. See Lawrence M. Blatt et al., *The Biologic Activity and Molecular Characterization of a Novel Synthetic Interferon-Alpha Species, Consensus Interferon*, 16 J. INTERFERON & CYTOKINE RES. 489, 491 (1996) (stating that Amgen's consensus interferon has an anti-viral activity as high as or higher than that of IFN- α 2); see also EDWARD DE MAEYER & JACQUELINE DE MAEYER-GUIGNARD, INTERFERONS AND OTHER REGULATORY CYTOKINES 28 (1988) (describing the "relatively low antiviral activity of Hu IFN- α 1" as compared to IFN- α 2).
130. To be sure, "infringement under the doctrine of equivalents is not precluded merely because the accused device performs functions in addition to those performed by the claimed device." *Insta-Foam Prods., Inc. v. Universal Foam Sys., Inc.*, 906 F.2d 698, 702 (Fed. Cir. 1990). The new property constituting a substantial improvement for purposes of infringement under the doctrine of equivalents must therefore be related to the purpose of the invention. For most gene and protein patents, any property relating to suitability for pharmaceutical use should be considered for purposes of known interchangeability.
131. *Genentech, Inc. v. Wellcome Found. Ltd.*, 14 U.S.P.Q.2d 1363, 1369 (D. Del. Mar. 8, 1990); see also *Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555, 1569 & n.42 (Fed. Cir. 1994).

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taining human t-PA muteins engineered to have longer half-lives—including several drugs sold by competitors, as well as Genentech's own TNKase—have come onto the market.¹³² That is a desirable outcome from the perspective of patent policy.

Many other cases will likewise be easier to resolve using the known interchangeability test than with the function-way-result test. For example, in *Roche v. Berlex*,¹³³ the arbitration involving a mutein with a single amino acid substitution, the modification rendered nonglycosylated human beta interferon suitable for pharmaceutical use. The function-way-result test is not very helpful here. The “function” of the claimed protein certainly includes the anti-viral activity characteristic of human beta interferon, but it is unclear whether suitability for pharmaceutical use is also part of the “function.” If the “function” is limited to anti-viral activity, it is not immediately apparent whether the higher specific activity of Berlex's mutein means that the mutein achieves that “function” in a different “way” or with a different “result.”

By contrast, the known interchangeability test provides a clear, sensible outcome. Berlex's mutein is the basis of a successful pharmaceutical product, whereas Roche's claimed protein has not been used commercially, presumably because of the very problem of stability associated with it that prompted the research leading to the creation of the mutein. On these facts, the two proteins are not interchangeable, and the mutein does not infringe under the doctrine of equivalents.

Of course, there will be borderline cases not easily resolved by the known interchangeability test. How great an increase in biological activity is required before the variant sequence is no longer interchangeable with the claimed sequence? Is 10% enough? How about 20% or 30%? There can be no bright-line answer, and the resolution of a close case will turn on the testimony of scientific, pharmaceutical or medical experts as to whether a person skilled in the art would consider the difference substantial. Doctrine of equivalents cases are inherently fact-intensive, and there is no mathematical test that will provide an easy answer in every instance.

132. Thus, in a case following *Genentech v. Wellcome*, 29 F.3d 1555 (Fed. Cir. 1994), involving a different human t-PA mutein, Genentech asserted various process patents but did not assert its patent on the human t-PA gene. *See Genentech, Inc. v. Boehringer Mannheim GmbH*, 47 F. Supp. 2d 91 (D. Mass. 1999).

133. *See supra* note 62.

VI. CONCLUSION

The known interchangeability test is well established in Supreme Court and Federal Circuit precedent and is particularly well suited to deciding doctrine of equivalents cases for gene and protein patents. Lawyers advising their clients on whether a gene or protein patent covers a mutein-based drug, and courts faced with such cases, will find that the known interchangeability test is analytically more useful in these situations than the function-way-result test that the Federal Circuit used in *Genentech v. Wellcome*. Under the known interchangeability test, gene and protein patents cannot be easily evaded by creating “neutral muteins,” but, at the same time, such patents will not cover muteins with substantially improved or new properties. Recognition of these basic principles would help to bring some predictability to this evolving area of patent law, and would protect and enable ongoing investment in the important work of developing “second generation” recombinant pharmaceutical products.