Appeal No. 2008-1248

In the
United States Court of Appeals
for the Federal Circuit

ARIAD PHARMACEUTICALS, INC.,
MASSACHUSETTS INSTITUTE OF TECHNOLOGY,
THE WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH, AND
THE PRESIDENTS AND FELLOWS OF HARVARD COLLEGE
Plaintiffs-Appellants

v.

ELI LILLY & COMPANY
Defendant-Appellee

Appeal from the United States District Court for the District of Massachusetts in Case No. 02-CV-11280, Judge Rya W. Zobel

BRIEF OF *AMICUS CURIAE* LAW PROFESSOR CHRISTOPHER M. HOLMAN IN SUPPORT OF NEITHER PARTY

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Dated October 13, 2009

CERTIFICATE OF INTEREST

Amicus Curiae Christopher M. Holman certifies the following:

1. The full name of every party or *amicus curiae* represented by me is Christopher M. Holman.

2. The name of the real parties in interest (if the party named in the caption is not the real party in interest) represented by me is Christopher M. Holman.

3. All parent corporations and any publicly held companies that own 10 percent of the stock of the party or *amicus curiae* represented by me are: None.

4. The names of all law firms and the partners or associates that appeared for the party or *amicus curiae* now represented by me in the trial court or are expected to appear in this court are:

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STATEMENT OF INTEREST OF *AMICUS CURIAE*

Amicus curiae is a professor who teaches and write about biotechnology patent law and policy. *Amicus* has a Ph.D. in molecular biology and extensive experience as a scientist and patent attorney working in the biotechnology industry. *Amicus* has no personal interest or stake in the outcome of this case. No part of this brief was authored by counsel for any party, person, or organization besides *amicus*. My sole interest in this case is maintenance and development of a sensible patent system that accurately reflects science and which provides appropriate incentives for innovation, particularly in biotechnology.

ARGUMENT

I. Introduction

Regents of the University of California v. Eli Lilly, 119 F.3d 1559 (Fed. Cir. 1997) established a novel interpretation of the written description requirement, referred to herein as Lilly written description (LWD), which unlike traditional written description applies to originally filed claims. The LWD test for "possession" has in the vast majority of cases been applied in a manner that is essentially redundant with the enablement requirement.[1] As noted by Judge Linn's concurrence in the case below, the adequacy of Ariad's disclosure could have been more appropriately assessed using the enablement requirement, and the same outcome might thereby have been arrived at in a more convincing fashion.[2]

However, LWD can and sometimes does function as a super-enablement requirement for patent claims reciting proteins and DNA sequences. With respect to these claims, LWD has sometimes been applied in a manner that imposes biotechnology-specific requirements of "possession" more stringent than the

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[1] Mark D. Janis, *On Courts Herding Cats: Contending with the "Written Description" Requirement (and Other Unruly Patent Disclosure Doctrines)*, 2 WASH. U. J.L. & POL'Y 55, 106-108 (2000); Timothy R. Holbrook, *Possession in Patent Law*, 59 SMU L. Rev. 123, 150-56 (2006); Christopher M. Holman, *Is Lilly Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of Eli Lilly and Its Progeny in the Courts and PTO*, 17 Alb. L.J. Sci. & Tech. 1 (2007).

[2] Holman's Biotech IP Blog, *Ariad v. Eli Lilly and In Re Kubin: One Federal Circuit Panel Perpetuates the Lilly Written Description Doctrine, While Another Avoids Addressing It*, http://holmansbiotechipblog.blogspot.com/search?q=ariad (visited October 9, 2009).

enablement requirement, referred to in this brief as the "species possession requirement" and the "genus possession requirement."[3] These biotechnology-specific possession requirements have been applied in an inconsistent and arbitrary manner lacking any basis in science, and at times precluding adequate patent protection for important inventions relating to proteins and DNA molecules.

Assessing the degree of disclosure necessary to support the patenting of biotechnological inventions, and achieving optimal claim scope for genus claims reciting proteins and DNA, are undoubtedly challenging and important issues that patent law must address in order to maintain adequate incentives for innovation without unduly inhibiting subsequent innovators. But the enablement requirement, which prior to *Lilly* was invoked as a potent and largely effective doctrinal tool for calibrating biotechnological patent claims to a scope commensurate with the disclosure, is better suited to the task. Enablement applies relatively objective standards, as exemplified by the *Wands* factors, which explicitly recognize and take into account factors such as the knowledge of one skilled in the art and the predictability of the technology, critical considerations in an evolving field such as biotechnology. *In re Wands*, 736 F.2d 1516 (Fed. Cir. 1984).

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[3] These terms have not been used by the courts or PTO, but reflect two distinct contexts in which LWD has been applied, and are used to facilitate the following discussion.

II. The Species Possession Requirement Imposes an Arbitrary, Discriminatory and Unjustified Super-Enablement Requirement on Some Biotechnological Inventors

Lilly held that the written description requirement requires a disclosure evidencing possession a species falling within the scope of a DNA claim, and by implication the requirement applies to chemical claims in general. *Lilly's* "species possession requirement" is analogous to the requirement that the disclosure enable one of skill in the art to make and use at least one species falling within the scope of a claim. In some cases, however, particularly with respect to DNA and proteins, this court and the PTO have applied the requirement in a manner that is more demanding than enablement, effectively rendering it a super-enablement requirement.

For some closely related molecules, for example antibodies, which are a type of protein, and genetically altered viral genomes, which are DNA molecules, this court and the PTO have effectively adopted the enablement standard for assessing compliance with the species possession requirement. *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004) (genus claim broadly reciting antibodies capable of recognizing a specific antigen satisfies LWD in the absence of a structural description or reduction to practice of any antibody falling within the scope of the claim, and without any disclosure of the structure of the antigen); *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1362, 1366 n.10 (Fed. Cir. 2006) (claim reciting

a poxvirus vaccine, made by deleting an essential gene from the viral genome, satisfies LWD even though the specification provided no structural description of the claimed viral genome, and the applicant had not produced any vaccine falling within the scope of the claim). Enablement is the appropriate standard, but it should be applied across the board to all biotechnology inventions.

Lilly was initially widely assumed to have created a super-enablement requirement "forcing biotech patentees to list particular gene sequences in order to obtain a patent covering of sequences."[4] In the first decision by this Court addressing LWD, *Enzo Biochem v. Gen-Probe*, 285 F.3d 1013 (Fed. Cir. 2002) (*Enzo I*), the panel initially applied a strict literal interpretation of *Lilly*, and invalidated DNA claims for failure to disclose the chemical structure of any species falling within the scope of the claim. However, the Court apparently came to appreciate the huge negative impact a literal interpretation of *Lilly* would have on biotechnology, and vacated its decision, reversing course and to a large extent repudiating *Lilly*. *Enzo Biochem v. Gen-Probe*, 323 F.3d 956 (Fed. Cir. 2002) (*Enzo II*). In *Enzo II*, the panel held that deposit of a DNA molecule to a publicly accessible depository satisfies the species possession requirement, essentially applying the conventional enablement standard. As noted by one commentator,

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[4] Mark A. Lemley & Dan L. Burk, *Policy Levers in Patent Law,* 89 Va. L.R. 1575, 1652-54 (2003). See generally Holman, *supra* note 1 at 18-20.

Enzo I was decided in a manner entirely consistent with *Lilly*, so by vacating and reversing the earlier decision this Court effectively acknowledged that *Lilly* itself must be wrong.[5]

A. *Wallach* exemplifies application of the species possession requirement as a super-enablement requirement

In re Wallach, 378 F.3d 1330 (Fed. Cir. 2004) provides an example of the species possession requirement being applied as a super-enablement requirement. Wallach had isolated and partially characterized a naturally occurring protein, and the PTO had explicitly found that the partial characterization of the protein was sufficient to render a claim reciting the protein patentable, even though the specification did not disclose the full structure of any protein falling within the scope of the claim. However, the examiner invoked LWD and rejected another claim reciting the DNA encoding the protein because the specification did not disclose the structure of the DNA. The applicant argued that the disparate treatment of DNA and protein claims was illogical, since one in possession of the protein could routinely and predictably isolate the corresponding gene sequence using conventional methodology. Nonetheless, the Board of Patent Appeals and Interferences (BPAI) and this Court affirmed the rejection.

This Court did not dispute Wallach's argument that the methodology for cloning and isolating the genus was conventional (and thus likely to be enabled).

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[5] MARTIN J. ADELMAN, 3-2 PATENT LAW PERSPECTIVES § 2.9 (2004).

In fact, in a subsequent decision, this Court explicitly held that the methodology for cloning a gene is predictable and conventional once the corresponding protein has been isolated, thus clearly implying that the disclosure of the partially characterized proteins and conventional methodology for isolating the corresponding gene satisfied the enablement requirement. *In re Kubin*, 561 F.3d 1351 Fed. Cir. 2009).

In *Wallach*, the species possession requirement denied patent protection to an inventor who had discovered, described and apparently enabled a novel and useful DNA sequence. *Wallach* offered no policy rationale for requiring more than an enabling disclosure for DNA claims.

In practice, the species possession requirement only appears to function as a super-enablement requirement for the very limited category of invention exemplified by *Wallach*, i.e., a newly discovered protein or DNA sequence. For other inventions, inventors are generally not required to reduce their invention to practice or describe their invention in highly specific structural terms in order to patent it, so long as the other patentability requirements are satisfied.

B. The species possession requirement arbitrarily and unjustifiably discriminates against some biotechnological inventors

Today, twelve years after *Lilly* was decided, this Court has yet to articulate a cohesive statement of the standard for satisfying the species possession requirement, and has applied it in an inconsistent manner to arrive at irreconcilable

outcomes for analogous inventions. In view of the lack of clarity and guidance from this Court, it is not surprising that the PTO has struggled in its attempts to interpret and apply *Lilly* and its progeny outside of the specific facts of those cases. As noted above, the heightened disclosure requirement of *Wallach* has not been applied to closely analogous biotechnological inventions involving antibodies and viral genomes.

For example, the current PTO Written Description Training Materials (the "Training Materials")[6] conclude that a broad genus claim reciting an "isolated antibody capable of binding to [a protein identified as] antigen X" satisfies LWD, even though the specification indicates that not one single antibody falling within the scope of the claim has ever been made, and provides no description of the structural, physical or chemical properties of any antibody falling within the scope of the claim. Training Materials Example 13.

Example 13 and *Wallach* are wholly inconsistent, essentially applying the conventional enablement requirement to antibodies but a heightened super-enablement requirement to other proteins and DNA in general. In *Noelle v. Lederman*, 355 F.3d 1343, 1349, this Court specifically adopted the PTO's dissonant treatment of antibodies, characterizing the antibody example in the Training Materials as "precedent." See also *Enzo II*, 323 F.3d at 967 (taking

[6] http://www.uspto.gov/web/menu/written.pdf (visited October 6, 2009).

judicial notice of the Training Materials).[7] *Noelle* provides no explanation for the entirely different standard applied to antibodies compared to other proteins and DNA.

Attempts by the PTO to justify the discrepancy merely serves to illustrate the illogic and unworkability of the species possession requirement, and LWD in general. For example, the Training Materials explain that in Example 13 the specification satisfies the species possession test because the various classes of antibodies share well-defined structural characteristics. But the PTO fails to recognize the significance of the fact that antibodies are known to comprise "constant regions" and "variable regions."[8] It is true that antibodies share well-defined structural characteristics in their constant regions, but that misses the point. The antibody claim in Example 13 defines the antibody solely in terms of the functional capability of binding to antigen X, and antigen-specific binding occurs in the variable region of the antibody, as specifically acknowledged in Example 13.

While the structure of conserved regions of antibodies might be well understood, the variable region can assume any of literally billions of chemical structures.[9] It is this extreme potential for structural diversity in the variable region

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[7] In these cases the Court was referring to an earlier version of the Training Materials, but the antibody example is substantially identical in both versions.
[8] JEREMY M. BERG ET AL., BIOCHEMISTRY 925 (2002 5th. Ed.).
[9] *Id.* at 929-34. See also http://en.wikipedia.org/wiki/Antibody (visited Oct. 6, 2009).

that confers upon an antibody the ability to recognize and selectively bind a specific antigen.[10] But since antigens vary dramatically in structure, antibody variable regions vary in a corresponding manner in order to recognize a specific antigen. Structural information relating to the conserved domains of known antibodies provides absolutely no information regarding the structure of the variable domain of an antigen to a novel protein of unknown structure.

The Training Materials also point to the fact that the methodology for making antigen-specific antibodies to an isolated protein antigen is routine. This is correct, but that is also the case for methodology employed in the cloning of a gene encoding an isolated and partially characterized protein. In the context of obviousness this Court recently affirmed the BPAI's factual finding that the methodology for isolating the DNA encoding a protein is "conventional" once the protein has been isolated. *Kubin*, 561 F.3d at 1356. In effect, the PTO (and this Court by endorsing the Training Materials as "precedent") applies the species possession requirement to antibodies in a manner that is redundant with the enablement standard, with the analysis turning on the predictability and conventional nature of the methodology for producing antibodies.

The PTO is correct in its ultimate conclusion that an antibody defined in purely functional terms can be patentable, so long as it is supported by an enabling

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[10] *Id.* at 927-29.

disclosure. It is in other cases, such as *Wallach*, in which a super-enablement requirement is arbitrarily applied to a very similar invention, where the PTO and this Court have been led astray in their quixotic attempt to apply LWD in a reasoned fashion. The gross inconsistency in the treatment of antibodies claims compared to other proteins and DNA merely illustrates the incoherence and unworkability of LWD as a doctrine of patentability.

III. The Genus Possession Requirement Imposes a Super-Enablement Standard on Some Biotechnological Inventions That Is Unsupported by Law, Science or Policy

Lilly created a "genus possession" requirement by holding that that a claim reciting a genus of related DNA molecules, and by implication chemical genus claims in general, must be supported by a disclosure evidencing possession of the genus. Unfortunately, as noted by at least one district court, "*Lilly* did not provide guidance as to 'the ways a broad genus of genetic material may be properly described.'" *Carnegie Mellon University v. Hoffmann La-Roche*, 148 F.Supp.2d 1004, 1016 (N.D.Cal. 2001), beyond a suggestion that the requirement could be satisfied by explicitly disclosing the chemical structures for a" representative number" of species falling within the scope of the claim, or by "recitation of structural features common to members of the genus." *Lilly*, 119 F.3d at 1568-69.

A typical biotechnology claim might recite all proteins sharing the function and at least 80% structural identity with a specifically identified protein. It is generally possible to substantially alter a protein's structure without necessarily destroying its function. For example, in some cases 50% percent or more of the amino acids in a protein can be altered while still maintaining function.[11] On the other hand, a single amino acid change can sometimes result in loss of function.[12] Thus, the genus of proteins sharing 80% structural identity with a functional protein will include many functional and non-functional variants. The LWD genus possession test has been interpreted by the PTO as requiring some level disclosure of the structure-function relationship that would allow one to distinguish *a priori* which variants sharing 80% or more structural identity will retain function, and this view has implicitly been endorsed by this Court when it characterizes the Training Materials as "persuasive authority" and "precedent."

A. In *Ex parte Kubin* the BPAI explicitly applied the genus possession requirement as a super-enablement requirement

In *Ex parte Kubin*, 2007 WL 2070495 (BPAI 2007), a rare precedential opinion by the BPAI, the species possession requirement was not at issue, because

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[11] *Id.*; BIOINFORMATICS FOR GENETICISTS Chapter 14 (Michael R. Barnes & Ian C. Gray eds., John Wiley & Sons, Ltd. 2003).

[12] Christopher M. Holman and William F. Benisek, *Insights into the Catalytic Mechanism and Active Site Environment of C. testosteroni Δ^5-3-Ketosteroid Isomerase as Revealed by Site-Directed Mutagenesis of the Catalytic Base Aspartate-38*, Biochemistry 34:14245-53 (1995).

the specification provided the chemical structure of a DNA molecule falling within the scope of the claim. However, the claim was not limited to that specifically disclosed polynucleotide, but also encompassed the genus of DNA molecules encoding functional variants sharing up to 80% structural identity with the disclosed protein. The examiner invoked the genus possession requirement to invalidate the claim under LWD, and the BPAI affirmed, holding that since the specification failed to identify which particular amino acids in the protein sequence were critical for function, the claim was not supported by a sufficient disclosure of the correlation between protein structure and function.

In *Kubin* the BPAI explicitly applied the genus possession requirement as a super-enablement requirement. The patent examiner had rejected the claim for failure to comply with both LWD and the enablement requirement. The BPAI reversed the enablement rejection, holding that the specification enabled one of skill in the art to make and identify functional variants extending throughout the scope of the claim without undue experimentation. However, the BPAI went on to hold that the genus possession requirement requires a more detailed description of the structure-function relationship, and affirmed the LWD rejection. The BPAI provided absolutely no guidance with respect to the amount of structure-function relationship necessary to satisfy the test, other than concluding that the test for

compliance with the genus possession test is more stringent than the enablement requirement, and that Kubin had somehow failed to meet the undefined standard.

This Court has never provided coherent guidance as to how much disclosure of the structure-function relationship is necessary, e.g., how many representative species or structural features are required to satisfy the test? As exemplified by *Kubin*, the PTO treats it as a super-enablement requirement, at least with respect to DNA and some protein inventions, and requires more disclosure of the structure-function relationship that would be necessary to enable the full scope of the claim. However, as explained below, the PTO apparently recognizes that it would be technologically impossible to provide anything approaching a complete description of the structure-function relationship for a genus of complex molecules such as proteins and DNAs, and thus does not require a complete description of the structure-function relationship across a claimed genus.

B. It is impossible for an inventor to provide anything approaching a complete description of the relationship between structure and function for a genus of complex molecules such as proteins or DNA

When this Court and the PTO apply the LWD genus possession requirement as a super-enablement requirement, they often fail to appreciate the nature of the relationship between structure and function in complex molecules such as proteins. It is generally impossible to confidently predict the effect of a change in structure on function, e.g., the substitution of one or more amino acids in the protein by

another, particularly when multiple changes in different locations are combined. As noted in a book on protein engineering scheduled for publication in 2010, "[d]espite recent advances in the field . . . protein engineering remains as much an art as it is a science . . . because the rules defining sequence-structure-function relationships are still not well understood."[13]

In part, the uncertainty results from the unfathomably large number of potential variants that can be generated by amino acid substitutions. For example, there are 1.8×10^{226} potential variants that share 80% or greater sequence identity with a 300 amino acid protein.[14] Astronomical does not even begin to describe the magnitude of this number. For comparison, it has estimated that there are about 10^{80} atoms in the entire universe. Of course, many of these variants will not be functional, if the change in structure destroys function. But molecular biologists know from experience that a substantial percentage of the variants will retain function, and even a tiny percentage would still result in an astronomical number of potential functional variants because of the manifold possibilities for change in structure.[15]

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[13] PROTEIN ENGINEERING AND DESIGN at vii (Sheldon J. Park Jennifer R. Cochran eds., CRC Press 2010).

[14] Christopher M. Holman, *Protein Similarity Score: A Simplified Version of the BLAST Score as a Superior Alternative to Percent Identity for Claiming Genuses of Related Protein Sequences*, 21 Santa Clara Computer & High Tech. L.J. 55, 71 n. 70 (2004).

[15] *Id.*

For this reason, scientists interested in identifying variants of a functional protein that retain that function create "libraries" of variants and "screen" those variants for those retaining function.[16] A library is a large number of protein variants sharing some degree of structural similarity, and screening refers to the process of empirically testing these variants to identify those variants retaining function, or perhaps even improved or different function. The state-of-the-art in protein engineering and design relies heavily on empirical approaches such as library screening, which would be unnecessary if it was possible to predict *a priori* the function of protein variants without actually making and testing them.[17] To the extent the LWD genus possession test requires a heightened disclosure of the structure-function relationship that accurately predicts which structural variants retain function, it is imposing a requirement that does not comport with the science and is technologically infeasible.

The LWD genus possession requirement is also applied in an arbitrary and discriminatory manner to protein and DNA inventions. It has been found inapplicable to chemical claims outside the realm of biotechnology. *Union Oil Company v. Atlantic Richfield*, 208 F.3d 989, 997 (Fed. Cir. 2000). Furthermore, it has not even been applied as a super-enablement to some proteins, such as antibodies (*Noelle* and the Training Materials, see Section II.B) and proteins that

[16] PROTEIN ENGINEERING AND DESIGN, *supra* note 13 at Chapter 4.
[17] *Id.*

have been functionally modified. See, e.g., *Invitrogen Corp. v. Clontech Laboratories*, 429 F.3d 1052 (Fed. Cir 2005).[18] In these instances, the courts are in effect applying the genus possession requirement in a manner redundant with the enablement requirement. This is the appropriate standard; the problem is the cases where LWD is applied as a super-enablement requirement.

The PTO likely decided not to apply the genus possession requirement to antibodies because it would have effectively precluded effective patent protection for monoclonal antibodies, which are extremely important in research, diagnostics and medicine. Many of the most important biologic drugs, such as Herceptin, used to treat breast cancer, are monoclonal antibodies, and prior to *Lilly* the PTO had a well-established policy of permitting broad genus claims on antibodies defined purely in functional terms. The decision not to apply LWD to antibodies achieves the right outcome, but unfortunately the PTO apparently feels compelled by *Lilly* to apply this unjustifiably stringent disclosure requirement on the other proteins and DNA.

The genus possession requirement can substantially impair the ability of some biotechnological inventors to secure adequate patent scope to protect their invention. Even though it is impossible to predict *a priori* which variants of a protein will retain function, a competing biotechnology company can easily use

[18] See also, generally, Holman, *supra* note 1.

technology such as library screening to produce a virtually unlimited number of redundant functional variants of a disclosed protein. That is the why biotechnological inventors strive for genus claims that extend to redundant functional variants of a disclosed protein or DNA. When the genus possession requirement is applied as a super-enablement requirement, as was the case in *Ex parte Kubin*, it limits the inventor of an important biotechnological innovation to a patent claim that can easily be designed around simply by creating a functional variant that is enabled by the specification but unpatentable under LWD.

This problem was alluded to in *Enzo II*, when an expert testified that "astronomical" numbers of mutated variations of the deposited sequence would fall within the scope of the claims, and that such broad claim scope is necessary to adequately protect the inventor from copyists who could otherwise make a minor change to the sequence and thereby avoid infringement while still exploiting the benefits of the invention. *Enzo*, 323 F.3d 966.[19]

C. Confused attempts by this Court and the PTO to apply the genus possession requirement have proven inconsistent and highlight the lack of any sound scientific underpinning for the doctrine

Inconsistent and incoherent application of the genus possession requirement is evident in many decisions of this Court and the PTO, as exemplified by a

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[19] *See also*, Holman, *supra* note 14 and Antony L. Ryan & Roger G. Brooks, *Innovation vs. Evasion: Clarifying Patent Rights in Second-Generation Genes and Proteins*, 17 BERKELEY TECH. L.J. 1265, 1276–1278 (2002).

comparison of *Capon v. Esshar*, 418 F.3d 1349 (Fed. Cir. 2005) and *Carnegie Mellon University v. Hoffmann La-Roche*, 541 F.3d 1115 (Fed. Cir. 2008) ("*Carnegie Mellon*"). Both cases involved claims reciting a genus of DNA constructs comprising two segments of DNA . In *Capon*, a claim recited a construct comprising a first segment encoding some portion of an antibody capable of binding an antigen [i.e., ***any*** antigen, which would include any protein], and a second segment encoding at least some portion of a protein that (1) is expressed on the surface of cells of the immune system and (2) triggers activation and/or proliferation of the cells. In a representative claim from *Carnegie Mellon*, the first DNA segment is a "conditionally controllable foreign promoter," and the second DNA segment is a bacterial gene encoding DNA Polymerase I. In *Capon*, the Court reversed a BPAI decision finding the claim invalid under LWD, while in *Carnegie Mellon* the court held that the claim satisfied LWD as a matter of law.

Carnegie Mellon attempts to reconcile the conflicting outcomes, pointing out that at the time of the *Capon* patent application more than a thousand DNA sequences encoding mouse antibodies were known, but that only three bacterial DNA Polymerase I genes had been cloned at the time the *Carnegie Mellon* application was filed. 541 F.3d at 1126. While this explanation has some superficial appeal, it actually makes no sense when one considers the nature of the proteins encoded by the claimed DNA sequences. As discussed in the previous

section, the defining characteristic of antibodies is extreme structural variability in the antigen-binding variable regions. Thus, the disclosure of thousands of mouse antibodies provides no real description of the correlation between structure and function in the variable antigen-binding region which is used to define the claimed DNA segment.

In contrast, DNA polymerase I is an enzyme. Unlike antibodies, all DNA polymerase I proteins retain essentially the same function, and because function as dictated by structure, there is a relatively strict correlation between structure and function in the class of bacterial DNA polymerase I proteins. This translates into a relatively well defined correlation between structure and function amongst the bacterial DNA polymerase I genes recited in the *Carnegie Mellon* claims. For example, the three bacterial DNA polymerase I genes known at the time of the Carnegie Mellon patent application share extensive structural similarity,[20] reflecting a relatively well-defined correlation between structure and function. As a result, the three bacterial DNA polymerase I genes provide a much better description of the correlation between structure and function in the claimed genus of DNA molecules than the mouse antibody sequences cited in *Capon*.

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[20] Struhl & Davis, *Conservation and DNA Sequence Arrangement of the DNA Polymerase I Gene Region from Klebsiella aerogenes, Klebsielola pneumoniae and Escherichia coli,* J. Mol. Biol. 141:343-368 (1980).

Furthermore, *Carnegie Mellon* fails to address the second claimed DNA segment in *Capon*, which is defined solely in terms of the location and function of a protein encoded by the DNA, i.e., the protein is expressed on the surface of cells of the immune system and able to trigger activation and/or proliferation of the cells. The fact that this extremely broad and entirely functional description of a DNA segment could satisfy the genus possession test, while a claim specifically reciting a relatively well-defined bacterial gene is invalid as a matter of law is but one of many examples of the incoherency and unworkability of the genus possession test and LWD in general.

In attempting to make sense of LWD, the PTO issued written description guidelines in 1999.[21] In 2008, the PTO issued the revised Training Materials which replaced and superseded the earlier guidelines. In many cases, the original and 2008 versions arrive at entirely different conclusions with respect to the patentability of essentially identical claims and specifications, as explained in detail on Holman's Biotech IP Blog.[22] The deep confusion and inconsistency at the PTO is symptomatic of the fundamental flaws in the doctrine itself.

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[21] *See Synopsis of Application of Written Description Guidelines, at* http://www.uspto.gov/web/offices/pac/writtendesc.pdf (visited Oct. 6, 2009).
[22] Holman's Biotech IP Blog, *PTO Issues Revised Written Description Guidelines, Further Muddying the Waters*, http://holmansbiotechipblog.blogspot.com/2008/04/pto-issues-revised-written-description.html (visited Oct. 6, 2009).

In its struggle to make sense out of the elusive genus possession requirement, the PTO has floundered and developed standards that are best characterized as "junk science." For example, Example 11A in the Training Materials finds a claim reciting DNA encoding functional variants of a disclosed protein sharing least 85% sequence identity with the disclosed protein to be invalid for failure to comply with the genus possession requirement. Example 11B finds the exact same claim valid.

Why the opposite outcomes? In Example 11A the specification explicitly discloses only a single protein structure, while the specification in Example 11B discloses the same single protein structure plus data from deletion studies that identifies two domains of the protein as critical to function, which the PTO concludes would allow one to predict which amino acids in the disclosed protein could be changed without loss of function. But the PTO's analysis fails to recognize the complex and unpredictable relationship between protein structure and function, and thus fails to comport with scientific reality.

The PTO correctly notes that in general, non-conservative amino acid changes are more likely to result in loss of function, and that some domains of a protein are more critically involved in function than others. But these general trends are anything but hard and fast rules. The scientific literature is full of examples where a single conservative amino acid change results in a dramatic loss

of function.[23] There are likewise many examples where alterations occurring far from any known functional domain can have a dramatic effect on function.[24] On the other hand, loss of function caused by a mutation in the most "critical" region of a protein can often be reversed by a second mutation that compensates for the first.[25] As a graduate student, *amicus* demonstrated that a conservative change at

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[23] Haller et al., *A single amino acid substitution in the viral polymerase creates a temperature-sensitive and attenuated recombinant bovine parainfluenza virus type*, Virology 288(2):342-50 (2001). (Single conservative amino acid substitution resulted in temperature sensitivity and attenuated function); Mooers et al., *Contributions of all 20 amino acids at site 96 to the stability and structure of T4 lysozyme*, Protein Science 18(5):871-80 (2009). ("It can be very misleading to simply assume that conservative amino acid substitutions cause small changes in stability, whereas large stability changes are associated with nonconservative replacements").

[24] Axe, *Extreme functional sensitivity to conservative amino acid changes on enzyme exteriors,*
J. Mol. Biol. 301(3):5 (2000). ("[H]ighly conservative replacements of exterior residues [was] found to cause complete loss of function. . . . Contrary to the prevalent view, then, enzyme function places severe constraints on . . . exterior non-active-site positions").

[25] Thompson, Jeremy R. et al., *Compensatory capsid protein mutations in cucumber mosaic virus confer systemic infectivity in squash (Cucurbita pepo),* J.Virol. 80(15):7740-3 (2006) (Single amino acid substitution results in loss of function, which was then restored by introduction of an additional, compensatory single amino acid substitution); Olivares, Isabel et al., *Tryptophan scanning mutagenesis of aromatic residues within the polymerase domain of HIV-1 reverse transcriptase: critical role of Phe-130 for p51 function and second-site revertant restoring viral replication capacity,* Virology 324(2):400-11 (2004) (Compensatory mutations result in restored protein function); Wang, Yaqing et al., *Intra-allelic suppression of a mutation that stabilizes microtubules and confers resistance to colcemid,* Biochemistry 43(28):8965-73 (2004); Liang, C. et al., *Mutations within four distinct gag proteins are required to restore replication of human immunodeficiency virus type 1 after deletion mutagenesis within the dimerization initiation site,*. J Virol. 73(8):7014-20 (1999).

the amino acid location absolutely required for enzymatic function in ketosteroid isomerase resulted in a *greater* loss of function than a non-conservative amino acid change at the same location, the opposite outcome from that predicted by the PTO's overly simplistic view that non-conservative changes are more likely to impact function, and this phenomenon occurs often.[26] The bottom line is, while the deletion studies cited in the example would provide some structure-function relationship, it is but the slightest tip of the iceberg, and does not identify regions of the protein that could or could not be altered without a loss of function.

Compounding the illogic of the outcome in Example 11B, note that the patent claim found to be patentable is not limited to conservative mutations, or mutations outside the identified functional domain, but would also encompass multiple non-conservative mutations in the functional domains, i.e., the mutations the PTO concluded would likely result in a loss of function.

IV. This Court Has Never Articulated a Rational Justification for Creating a Super-Enablement Requirement For Some DNA and Protein Inventions

Lilly cites only two earlier Federal Circuit decisions as allegedly providing some sort of precedent for the species and genus possession tests, *Fiers v. Revel*,

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[26] See Holman and Benisek, *supra* note 12 (replacing an aspartic acid required for protein function with a glutamic acid (another acidic amino acid, conservative change) resulted in lower functional activity than replacement by histidine (a basic amino acid, non-conservative change).

984 F.2d 1164, 1171 (Fed. Cir. 1993) and *In re Smythes*, 480 F.2d 1376, 1383 (Cust. & Pat. App. 1973). Both cases addressed the test for conception of an invention in a highly unpredictable area of technology, but in *Lilly* this court unwisely used these decisions to justify a rule of disclosure divorced from any inquiry into predictability.

Smythe is not even a chemical case, but in dicta opines that "[i]n other cases, particularly but not necessarily, chemical cases, where there is *unpredictability in performance* of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a [genus] claimed at a later date." 480 F.2d at 1383 (footnote omitted, emphasis added). Thus, the statement in *Smythe* relates to the standard for assessing possession of an *unpredictable* invention for the purpose of demonstrating priority, not the standard for assessing possession of a chemical invention.

The focus in *Fiers* was also on the unpredictability of the science, but to fully understand *Fiers* and the genesis of LWD it is necessary to understand *Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991) (*Amgen*). In *Amgen*, the defendant attempted to invalidate a patent claiming the gene encoding human erythropoietin by arguing prior conception of the invention by one of its own scientists. The district court rejected this argument, finding that the scientist's mere plan to isolate

the gene did not constitute conception of the gene because at that time of alleged conception the technology for isolating a gene was unpredictable, and thus there was no reason to think that the attempt would be successful. *Amgen v. Chugai*, 1989 WL 169006 *33 (D.Mass. 1989).

On appeal, this Court affirmed the district court's ruling based on the unpredicability of cloning technology at the time of invention, holding that "given the utter lack of experience in [using the proposed methodology] and the crudeness of the techniques available in 1991, it would have been mere speculation or at most a probable deduction from facts and then known by [the GI inventor] that his generalized approach would result in cloning the [erythropoietin] gene." Unfortunately, the *Amgen* panel went on to state that "[c]onception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it." This is the seed from which he species possession test eventually sprouted six years later in *Lilly*.

Amgen does not cite any precedent supporting its assertion that a disclosure of chemical structure is necessary in order to establish conception. It cites *Oka v. Youssefyeh*, 849 F.2d 581, 583 (Fed. Cir. 1988) for the proposition that "[c]onception requires both the idea of the invention's structure and possession of an operative method of making it." However, *Oka* was the appeal of a priority

contest involving an inventor who had explicitly identified the chemical structure of his invention in the priority application; the case has nothing to say on the question of whether a description of chemical structures necessary, but it was apparently the closest precedent the *Amgen* panel could identify.

Ironically, *Amgen* also cited *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986) as somehow supporting a rule that a disclosure of chemical structure is necessary to establish conception. *Hybritech* held that the conception of a method of using a specific type of antibody had been established even though the disclosure provided absolutely no structural description of any antibodies falling within the scope of the claim and there was no actual reduction to practice.

Which bring us to *Fiers*, wherein a party to an interference sought to establish priority by claiming priority back to an earlier filed patent application that disclosed a plan for isolating the claimed gene but did not disclose the gene's structure. The Board denied the priority claim, citing *Amgen* for the rule that a disclosure of structure is required for conception of DNA, and holding that "[l]ogically, one cannot *reduce to practice or enable* an invention that has not been conceived." *Fiers v. Revel*, 1991 Pat. App. LEXIS 44 at *13 (BPAI 1991) (emphasis added).

On appeal, this Court could have simply affirmed the BPAI's conclusion based on the failure of the priority application to enable the invention. Instead, the panel gratuitously created a novel, DNA specific interpretation of the written description requirement, holding that "if a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a *description* also requires that degree of specificity. To *paraphrase* the Board, one cannot *describe* what one has not conceived. 984 F.2d at 1171 (emphasis added).

In *Lilly* the Court justified the species possession requirement in part by implying that a disclosure of chemical structure in the prior art is necessary to render a DNA sequence obvious, citing *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) and *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993), and reasoned that "*a fortiori,* a description that does *not* render a claimed invention obvious does not sufficiently describe that invention for purposes of § 112, ¶ 1." However, this questionable justification was recently effectively repudiated in *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009), wherein this Court held that a disclosure of structure is not necessary to render genetic DNA obvious if the prior art provides the motivation and predictable methodology for isolating the DNA. *Kubin* dispels the notion that a disclosure of chemical structure is necessary to render a DNA sequence obvious, entirely undercutting the contention in *Lilly* that the species possession requirement

provides symmetry between the requirements for obviousness under of § 103 and disclosure under § 112, ¶ 1.

The only real attempt at a policy justification provided in *Lilly* was the statement that "[a] definition by function . . . does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." This is incorrect as a matter of science. "A gene that controls blood sugar level" would be functional definition, since it does not identify a particular protein or gene. In contrast, the term "human insulin gene" describes a specific gene that was known to exist at the time of the patent application.

V. The Enablement Requirement Is the Appropriate Test for Adequate Disclosure Across All Technologies

The enablement doctrine requires the scope of a patent claim to "bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re* Fisher, 427 F.2d 833, 839 (C.C.P.A. 1970). The enablement requirement has often been used to police against overly broad claims in the context of biotechnology and molecular biology.[27] For example, in *Amgen* this Court invoked the "reasonable correlation" test to invalidate a claim reciting DNA molecules encoding functional variants of a disclosed protein, i.e., the exact sort of claim to which today the genus possession

[27] Holman, *supra* note 1 at 8-13.

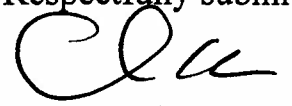
requirement is being applied. 927 F.2d at 1214. *Amgen* demonstrates that the enablement requirement is perfectly capable of policing against overly broad biotechnology claims. But unlike LWD, enablement has a relatively well-developed body of case law and accepted criteria for assessing the enablement of a claim. The "undue experimentation" standard, for example, and the relevance of predictability in assessing enablement under *Wands* are flexible and can evolve along with technology, unlike the rigid and inconsistent focus on structure which characterizes LWD.

While the outcomes in the *Amgen-Fiers-Lilly* trilogy might have been appropriate in view of the unpredictability of cloning technology at the time, LWD has locked biotechnological patent law into a strict requirement of structural disclosure or physical possession that is no longer warranted as the technology has become conventional and relatively predictable. Just as in *Kubin* this Court chose to discard the strict requirement of structural disclosure in the obviousness determination arguably required by *Bell* and *Deuel*, it should do away with LWD and its irrational focus on structure, and employ the more adaptable and appropriate enablement requirement to assess adequate disclosure of biotechnological and other inventions.

CONCLUSION

For these reasons, this Court should rule that there is no *Lilly* written description requirement applicable to originally filed claims.

Respectfully submitted,



Christopher M. Holman
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October 13, 2009

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the foregoing Brief of *Amicus Curiae* Law Professor Christopher M. Holman in Support of Neither Party was served on this 14TH day of October, 2009, by electronic mail and U.S. Postal Service First Class Mail on the following counsel of record:

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CERTIFICATE OF COMPLIANCE

Pursuant to Rule 32(a)(7)(C) of the Federal Rules of Appellate Procedure, I certify that the foregoing Brief of *Amicus Curiae* Law Professor Christopher M. Holman in Support of Neither Party complies with the type volume limitations of Rule 29(d) of the U.S. Court of Appeals for the Federal Circuit. I further certify that the body of this brief – not including the cover page, table of contents, table of authorities, Appendix, and certificates – contains 6982 words as determined by Microsoft Word 2003, including the statement of interest, summary of argument, headings, footnotes, quotations, signature lines, and date.

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