UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 02-11280-RWZ

ARIAD PHARMACEUTICALS, INC.,
MASSACHUSETTS INSTITUTE OF TECHNOLOGY,
THE WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH,
and THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE

v.

ELI LILLY & CO.

FINDINGS OF FACTS AND CONCLUSIONS OF LAW

July 6, 2007

ZOBEL, D.J.

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I. Introduction

Plaintiffs Ariad Pharmaceuticals, Inc., Massachusetts Institute of Technology, the Whitehead Institute for Biomedical Research, and the President and Fellows of Harvard College (collectively "Ariad"), owners and assignees of U.S. Patent No. 6,410,516 ("the '516 patent"), "Nuclear Factors Associated With Transcriptional Regulation," complain that defendant Eli Lilly & Co. ("Lilly") infringed it. Following a fourteen-day trial in April 2006, a jury found that the four asserted claims were valid against anticipation, enablement and written description defenses, and that use of Lilly's Evista and Xigris products infringed the patent. The jury awarded plaintiffs damages in excess of $65 million.

The parties agreed that certain additional defenses were to be tried to the court. Lilly asserts that the '516 patent is invalid because it attempts to claim non-patentable subject matter under 35 U.S.C. § 101. Even if the patent is valid, Lilly argues (1) that it cannot be enforced because of inequitable conduct by plaintiffs during the prosecution of the patent, or in the alternative; (2) that plaintiffs are estopped from recovering for any infringement because they unreasonably delayed prosecution of the patent.[1] Following a second trial focused on these issues, I find that: (1) the four claims

[1] Lilly also indicated in an August 1, 2006, pre-bench trial status conference that it believed the '516 patent claims asserted in this case are invalid because they do not satisfy the definiteness requirement of 35 U.S.C. § 112. However, neither its pretrial brief (Docket # 362) nor its proposed findings of facts (Docket # 397) discusses this issue. In addition, Lilly presented no evidence or argument on the issue of indefiniteness during the bench trial. Therefore, I do not address the indefiniteness of the claims further in this opinion.

asserted are patentable; (2) Lilly has not proven inequitable conduct during patent prosecution; and (3) Ariad did not unreasonably delay prosecution of the '516 patent. Accordingly, the jury award stands.

II. Background of the Case

A. Ariad's Invention

In the mid-1980s, scientists at the Massachusetts Institute of Technology, the Whitehead Institute for Biomedical Research, and Harvard University ("plaintiff institutions") identified a protein called Nuclear Factor Kappa B ("NF-κB"). Present in the cytoplasm of many different cell types, NF-κB is what is known as a transcription factor, a protein that affects gene expression.[2] In the inactive state, NF-κB binds in the cytoplasm with another protein, Inhibitor Kappa B ("IκB"), to form a multi-protein complex.[3] When NF-κB is activated by various stimuli external to the cell, the complex dissociates and free NF-κB is released. This free NF-κB then travels into the cell nucleus and binds there to specific DNA sequences, causing the cell to produce proteins that are associated with many diseases, including cancer, AIDS, sepsis, and atherosclerosis. Inhibiting this process has enormous and wide-ranging therapeutic effects.

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[2] Gene expression is the process in which a gene's DNA sequence is converted into a protein in a cell. Transcription refers to the step in this process by which a messenger RNA molecule is synthesized on the DNA template to transfer genetic information from the DNA to the RNA. Stedman's Medical Dictionary (27th ed. 2000).

[3] There are several IκB proteins, including IκB-α and IκB-β, that bind to NF-κB and inhibit its activity. (Defendant's Trial Exhibit ("DTX") 24-S at 653-54.)

The inventors filed a patent application on their invention. After a sixteen year trek through the United States Patent and Trademark Office (the "PTO") littered with abandoned, divisional and continued applications, they were granted the '516 patent on June 25, 2002.[4] Throughout much of the prosecution history of the '516 patent, questions concerning enablement under 35 U.S.C. § 112 delayed allowance,[5] in many instances because the claims called for the use of an "agent" or "substance" to effect a reduction or alteration in the level of NF-κB activity in the cell. The PTO repeatedly rejected these claims because it said that the specification did not adequately describe all possible agents or substances encompassed by the claims.

B. Obtaining Allowance

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[4] The complexity of the prosecution of the '516 patent is captured in the Related Applications section:

> This application is a division of application Ser. No. 08/418,266 filed Apr. 6, 1995, U.S. Pat. No. 5,804,374 which is a continuation of U.S. Ser. No. 07/791,898, filed Nov. 13, 1991, abandoned which is a continuation-in-part of U.S. Ser. No. 06/946,365, filed Dec. 24, 1986, abandoned and of U.S. Ser. No. 07/318,901, filed Mar. 3, 1989, abandoned and of U.S. Ser. No. 07/162,680, filed Mar. 1, 1988, abandoned and of U.S. Ser. No. 07/341,436, filed Apr. 21, 1989, abandoned and of U.S. Ser. No. 06/817,441, filed Jan. 9, 1986, abandoned and of U.S. Ser. No. 07/155,207, filed Feb. 12, 1988, abandoned and of U.S. Ser. No. 07/280,173, filed Dec. 5, 1988, abandoned.

('516 Patent col.1 ll.5-17.) Plaintiffs claim the benefit of priority of all of these applications and incorporate all of them by reference into the '516 patent.

[5] Title 35 U.S.C. § 112 states: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

On August 10, 2000, the primary examiner of the '516 application, Dr. Robert Schwartzman ("Schwartzman"), rejected all but one claim of the pending application as not adequately describing the agents used in claims drawn to methods requiring "an agent which has an effect on . . . NF-κB and/or IκB." (DTX 2 at ADL823-33, ADL825.)[6] In response, Ariad sent the PTO a reply on September 12, 2001, canceling all previous claims. It replaced the canceled claims with a new set of claims, 158-87, that did not require the use of agents to practice the claimed methods, along with six new claims, 188-93, that did include a limitation for the "administration of an agent . . ." to implement the method of claims 158-75. (Id. at ADL872-88, ADL876-78.) Two days later, in a telephone interview with Examiner David Guzo ("Guzo"),[7] Ariad's attorney authorized an examiner's amendment to, inter alia, cancel claims 188-193, the claims requiring the use of an agent. (Id. at ADL923-53, ADL924.) The remaining claims were subsequently allowed as amended by Guzo on October 4, 2001. (Id. at ADL923.)

The allowed claims broadly cover a method of inhibiting the expression of a gene whose transcription is regulated by NF-κB in a eukaryotic cell.[8] The only step required to practice the broadest patented method is to "reduc[e] NF-κB activity in the

[6] Pages in exhibit DTX 2, the '516 patent prosecution history, are marked in the form "ADL0000XXX." In citations to DTX 2, the court has dropped the leading zeros in each page number.

[7] Examiner Guzo was supervised by Examiner Schwartzman.

[8] A eukaryotic cell is a cell containing a nucleus and is typical of all multi-celled organisms as well as some single-celled organisms.

cell such that the expression of said gene is inhibited."[9] No particular agent or substance need be used, nor any particular step(s) performed, to reduce NF-κB activity in order to practice the invention.

C. Lilly's Drugs

Prior to the initial discoveries by the research team at plaintiff institutions, defendant Lilly applied for patents on two compounds, raloxifene hydrochloride and recombinant human activated Protein C ("aPC").[10] As it happens, these two compounds inhibit NF-κB activity, although Lilly did not know this when it obtained its patents. Lilly began marketing raloxifene hydrochloride under the brand name Evista to treat osteoporosis and has been selling aPC under the name Xigris to treat severe sepsis. At the molecular level, these drugs treat osteoporosis and severe sepsis, respectively, by inhibiting NF-κB activity.

D. Commencement of Litigation

On the same day that the '516 patent was granted, Ariad filed the instant suit against defendant Lilly, alleging that Lilly's sales and marketing of Evista and Xigris constituted indirect infringement of twenty claims of the '516 patent. Lilly filed a Combined Motion to Dismiss and Motion for Summary Judgment of Invalidity, contending that the earlier patents on its compounds anticipated the '516 patent and

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[9] See '516 Patent claim 1 ("1. A method for inhibiting expression, in a eukaryotic cell, of a gene whose transcription is regulated by NF-κB, the method comprising reducing NF-κB activity in the cell such that expression of said gene is inhibited.") (emphasis added).

[10] Raloxifene hydrochloride is covered by United States Patent No. 4,418,068, issued Nov. 29, 1983. The patent for aPC is No. 4,775,624, issued Oct. 4, 1988.

that the methods necessary to practice the '516 patent were not enabled by the written description. I denied the motion but noted that the problem of enablement was troubling, given the broad claim language and the question whether the patent described actual methods for inhibiting NF-κB activity. Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co., Civ. No. 02-11280, 2003 WL 21087115, at *1 (D. Mass. May 12, 2003) (Docket # 33).

Late in the discovery process, Lilly petitioned the PTO to reexamine the '516 patent pursuant to 35 U.S.C. § 302,[11] arguing that a large number of the patent's claims "encompassed numerous prior art methods employing compounds now known to necessarily modulate NF-κB activity." Lilly Request for Reexamination, Case No. 05-280, April 4, 2005, at 1. Lilly moved to stay the litigation pending the outcome of the PTO's reexamination, a motion I subsequently denied, as I was not persuaded that reexamination would simplify the issues for trial. Ariad Pharmaceuticals, Inc. v. Eli Lilly and Company, Civ. No. 02-11280, 2005 WL 1342721, at *1 (D. Mass. June 06, 2005) (Docket # 149). Lilly renewed its motion on January 17, 2006, after the PTO granted the reexamination request. I again denied the motion, and the case went to trial in April 2006.

E. The Jury Trial

After a fourteen-day trial, the jury determined that none of the four claims

[11] Title 35 U.S.C. § 302 provides in pertinent part: "Any person at any time may file a request for reexamination by the Office of any claim of a patent on the basis of any prior art cited under the provisions of section 301 of this title . . . ." 35 U.S.C. § 302 (2002).

ultimately asserted were anticipated, either by prior art or public use, and it found all the asserted claims adequately enabled and the written description adequate. The jury further found that a user of Evista directly infringed claims 80 and 95 of the '516 patent and that a user of Xigris directly infringed claims 144 and 145 of the patent.[12] It also found Lilly liable for inducing infringement and contributory infringement by selling the two drugs. The jury determined the effective filing date of the patent to be April 21,

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[12] The four '516 patent claims found infringed (emphasized and grouped with the claims on which they depend) are:

> 7. A method for modifying effects of external influences on a eukaryotic cell, which external influences induce NF-κB -mediated intracellular signaling, the method comprising altering NF-κB activity in the cells such that NF-κB-mediated effects of external influences are modified.
>
> 8. The method of claim 7, wherein NF-κB activity in the cell is reduced.
>
> 80. The method of claim 8 wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.
>
> 9. A method for reducing, in eukaryotic cells, the level of expression of genes which are activated by extracellular influences which induce NF-κB -mediated intracellular signaling, the method comprising reducing NF-κB activity in the cells such that expression of said genes is reduced.
>
> 95. The method of claim 9, carried out on human cells.
>
> 14. A method for reducing bacterial lipopolysaccharide-induced expression of cytokines in mammalian cells, which method comprises reducing NF-κB activity in the cells so as to reduce bacterial lipopolysaccharide-induced expression of said cytokines in the cells.
>
> 144. The method of claim 14 wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.
>
> 145. The method of claim 14, carried out on human cells.

1989, and awarded Ariad a royalty of 2.3% on combined sales by Lilly of over $2.83 billion, or over $65 million in damages, as of May 4, 2006.

F. Post-Verdict Motions

Lilly contends that this award must be set aside because either the '516 patent is invalid, as it claims subject matter not allowed under 35 U.S.C. § 101,[13] or because the patent cannot be enforced as plaintiffs committed a culpable breach of the duty of disclosure and unreasonably delayed prosecution. The parties agree that these issues raise questions of fact and law for the court. See Arrhythmia Research Technology v. Corazonix Corp., 958 F.2d 1053, 1055 (Fed. Cir. 1992) ("Whether a claim is directed to statutory subject matter is a question of law."); Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found., LP, 422 F.3d 1378, 1385 (Fed. Cir. 2005) ("[Prosecution laches] is to be decided as a matter of equity, subject to the discretion of a district court before which the issue is raised.").

G. The Bench Trial

A four-day bench trial addressing these issues began on August 7, 2006. Shortly before the commencement of that trial, the PTO, on August 2, 2006, issued a first Office Action in the merged ex parte reexamination proceeding that rejected 160 of the claims in the '516 patent, including the four at issue in this case.[14] (Office Action in

[13] Title 35 U.S.C. § 101 states: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

[14] In May 2006, the PTO merged Lilly's request for reexamination with a reexamination request of the '516 patent by Bawa Biotechnology Consulting, LLC.

Ex Parte Reexamination, Patent 6410516, August 2, 2006 (DTX 973A).) The PTO based its rejections partially on a determination that the claims were inherently anticipated by certain prior art references listed in a review article co-authored by Dr. Albert Baldwin ("Baldwin"), one of the inventors of the '516 patent.[15] In its claim of inequitable conduct, Lilly also charged Baldwin with intentionally withholding this information from the PTO.

I examine each of Lilly's defenses below.

III. Discussion

A. Validity of the Patent Under 35 U.S.C. § 101

In Lilly's view, the '516 patent claims subject matter not allowed under 35 U.S.C. § 101 and is therefore invalid. Specifically, it contends that the claims encompass the NF-κB-IκB autoregulatory loop (the "Autoregulatory Loop"), a natural process in cells that operates to reduce the activity of NF-κB. Because natural phenomena are excluded from patentable subject matter, it argues that any '516 claims encompassing the Autoregulatory Loop are invalid and cannot be enforced.

Ariad's response is that the '516 patent does not claim a natural phenomenon because, inter alia, (1) the patent claims a process, subject matter specifically allowed by statute; and (2) the Autoregulatory Loop is only a theory and has not been proven to exist in human cells in vivo. (Docket # 398 ¶ 618.) While not all processes are

[15] The PTO's rejection of Ariad's claims does not end the re-examination. Rather, it is merely an early step in the process. Ariad may respond to the prior art, propose amendments to its claims, or appeal the PTO's decision. See 35 U.S.C. §§ 301-306.

patentable, I find that Lilly has failed to show that the proposed model of the Autoregulatory Loop actually exists in nature and thus that a natural phenomenon is encompassed by the '516 patent's claims.

1. Exceptions to Patentable Processes

Ariad insists that an analysis of the scope of the patent's claims is not relevant to a determination of whether the patent claims unpatentable subject matter. It argues that because the '516 patent claims describe the transformation of the activity state in cells, they meet the definition of a process, subject matter specifically allowed under 35 U.S.C. § 101, and the subject matter analysis ends. In its view, any consideration of the scope of the claims only affects whether the claims are anticipated or properly disclosed, issues already decided in its favor by the jury. (See Docket # 398 ¶¶ 572-83, 597-602.) This position, however, oversimplifies the law.

Congress has broadly defined the subject matter that can be protected by patent. Title 35 U.S.C. § 101 states simply that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter . . . may obtain a patent therefore . . . ." The Committee Reports accompanying the Patent Act of 1952 emphasized the breadth of this statutory subject matter as "includ[ing] anything under the sun that is made by man." Diamond v. Dier, 450 U.S. 175, 182 (1981) (quoting S. Rep. No.1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No.1923, 82d Cong., 2d Sess., 6 (1952)). "Process," as used in the statute, is synonymous with

"method"[16] and means "a mode of treatment of certain materials to produce a given result." Id. at 182.

Three exceptions exist, however, to the general principle that any process is eligible for patent protection: "laws of nature, natural phenomena, and abstract ideas." Id. "The rule that the discovery of a law of nature cannot be patented rests, not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of 'discoveries' that the statute was enacted to protect." Parker v. Flook, 437 U.S. 584, 593 (1978). A process, however, is not unpatentable merely because it contains a law of nature; a process employing a law of nature or natural phenomena in a useful way may be protected by patent. Id. at 592 (distinguishing Morse's invalid claim, broadly covering the use of electromagnetism to print at a distance, from Neilson's allowed claim for a machine applying the principle that heated air increases the intensity of the heat in a blast furnace). The court must examine what is sought to be patented in order to determine whether it falls within one of the statutory exceptions. This determination occurs before any consideration whether that discovery meets the requirements for patentability under 35 U.S.C. §§ 102, 103 and 112.[17] Id. at 593 ("The obligation to determine what type of discovery is

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[16] See 35 U.S.C. § 100(b) ("The term 'process' means process, art or method . . .").

[17] Ariad's reliance on statements by the Federal Circuit disavowing scope as relevant to section 101 analysis is misplaced. The discussion cited by Ariad in State Street concerned whether § 101 prevented the inventor from claiming so broadly as to block other potential inventions, not subject matter; the court had already considered subject matter and concluded that the claims were not directed toward "an unpatentable abstract idea." State Street Bank & Trust Co. v. Signature Fin. Group, Inc., 149 F.3d

sought to be patented must precede the determination of whether that discovery is, in fact, new or obvious.").

Therefore, the asserted claims must be examined to see if they encompass any of these exceptions. If Ariad's claims are drafted so broadly that they encompass a natural process, they are invalid for claiming unpatentable subject matter.

2. The Autoregulatory Loop Theorizes a Reduction in NF-κB Activity

As noted above, Lilly argues that Ariad's asserted claims encompass a natural phenomenon, the Autoregulatory Loop. Lilly's scientific expert, Dr. David Latchman ("Latchman") described the Autoregulatory Loop as a natural process by which the activity of NF-κB in a cell is controlled by IκB-α via negative feedback. (Trial Tr. Day 1, 48:23-52:1.)[18] This process is triggered when an external stimulus causes NF-κB to disassociate from IκB in the cytoplasm of the cell. Free NF-κB then moves into the nucleus and binds to the cell's DNA. The bound NF-κB stimulates the production of

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1368, 1374-77 (Fed. Cir. 1998) (refusing to find as unpatentable claims which, it was argued, were "sufficiently broad[] to foreclose virtually any computer-implemented accounting method . . . ."). The issue in SmithKline concerned whether the inevitable production of a previously patented synthetic substance as a by-product of the manufacture of a newly discovered man-made compound should be considered "naturally occurring" under § 101. SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1342 (Fed. Cir. 2005). In neither case was the court simply considering whether the scope of the claims at issue encompassed a natural phenomenon. Cf. In re Bergstrom, 427 F.2d 1394, 1401 (C.C.P.A. 1970) (noting "appellants have neither merely discovered, nor claimed sufficiently broadly to encompass, what has previously existed in fact in nature's storehouse, albeit unknown," in concluding patented substance was not naturally occurring) (emphasis added).

[18] Citations to "Trial Tr." refer to the bench trial held August 7 through August 10, 2006.

various proteins in the cytoplasm, including certain cytokines,[19] but it also causes the production of new IκB. This newly produced IκB reenters the nucleus of the cell and removes the bound NF-κB from the DNA, deactivating it and terminating production of the gene for the induced proteins. The deactivated NF-κB/IκB complex then moves out into the cytoplasm completing the regulatory loop. The NF-κB that was activated by the external stimulus has been deactivated by the IκB that it caused to be generated, naturally terminating the externally induced response. (Id.; see also DTX 3037 (demonstrative video).)

a. Support for the Existence of the Autoregulatory Loop

The possibility of an NF-κB--IκB regulatory loop was unknown in 1991 when the '516 specification was initially submitted to the PTO and thus is not described in the issued patent.[20] (See DTX 33, ADL14830-ADL15018 (specification filed Nov. 13, 1991 with application 07/791,898).) Latchman testified that reports on the existence of the Autoregulatory Loop first appeared in three papers published in 1993. (Trial Tr. Day 1, 99:17-100:9.) He cited a number of more recent articles as also supporting his description of the Autoregulatory Loop, including a 1996 review paper by co-inventor

[19] Cytokines are secreted proteins that affect the functions of other cells and which are important for the interactions between cells in the immune response. (Docket # 69, 12 n.9; Hr'g Tr., 57:9-11, Jan. 13, 2004.)

[20] The 1991 application was a continuation-in-part of an earlier application, 07/341,436, which was ultimately abandoned. The jury found the effective filing date of the '516 patent to be April 21, 1989, the date of this earlier application.

Baldwin. (Id. at 54:22-589:19; DTX 24-S.)[21] Latchman also discussed at length an article by Ting & Endy describing the operation of the Autoregulatory Loop. (Trial Tr. Day 1, 60:5-75:10; DTX 469A.)[22] This paper was published as a "Perspective" article to comment on a longer article, published in the same issue of Science, authored by Dr. Alexander Hoffman ("Hoffman") and, inter alia, co-inventor Dr. David Baltimore ("Baltimore"). (DTX 469.)[23]

As explained by Latchman, Ting & Endy described the operation of the Autoregulatory Loop based on Hoffman's experiments comparing cells from natural mice ("wild type") with cells from genetically engineered "knockout" mice. These so-called "knockout cells" have copies of the gene for IκB inactivated, so that there is no functional IκB-α in the cells. (Trial Tr. Day 1, 58:2-10, 64:13-17.) In wild type cells, a temporary external stimulus of TFN[24] results in only a short period in which NF-κB is present in the nucleus of the cell and in no production of RANTES, a gene activated only after prolonged exposure to NF-κB. The induced active NF-κB is quickly deactivated by new IκB-α produced by the binding of the NF-κB to the DNA before the

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[21] Albert Baldwin, Jr., The NF-κB and IκB Proteins: New Discoveries and Insights, 14 Ann. Rev. Immunol. 649, 666 (1996) ("These results indicate that NF-κB and IκB are components of a mutual regulatory system in which the levels of one regulatory component control the activity or quantity of the other.").

[22] Alice Y. Ting & Drew Endy, Decoding NF-κB Signaling, 298 Science 1189 (2002) ("Ting & Endy").

[23] Hoffmann et al., The IκB-NF-κB Signaling Module: Temporal Control and Selective Gene Activation, 298 Science 1241 (2002).

[24] TFN is an inducer cytokine used by Hoffman to switch on NF-κB. (Trial Tr. Day 1, 64:21-23.)

RANTES gene is expressed. In knockout cells without the ability to produce IκB-α, a temporary external stimulus of TFN results in a prolonged period in which NF-κB is present in the nucleus of the cell and in the eventual production of the RANTES gene. (Id. at 64:11-69:24.) Unlike the wild type, the level of NF-κB bound in the nucleus of the knockout cell is not reduced by the production of IκB-α, allowing time for the RANTES gene to be induced. In Latchman's opinion, this demonstrates the ability of the Autoregulatory Loop to inhibit induced gene expression. (Id. at 69:25-70:3.) Latchman described the results of additional experiments in which the external stimulus was sustained over a period of time. Even with a continuous stimulus, he asserted that the Autoregulatory Loop operates to reduce the level of NF-κB mediated gene expression in the wild cells, albeit in an oscillatory fashion. (Id. at 66:10-23, 73:15-74:10.)

b. Testimony of Ariad's Expert, Dr. Ravetch

Ariad's expert, Dr. Jeffrey Ravetch ("Ravetch"), objected to Latchman's conclusion that the Autoregulatory Loop has been proven to exist in living cells. (Trial Tr. Day 3, 10:17-21.) He described the Autoregulatory Loop as a simplified model that poorly explains the experimental data. (Id. at 17:13-18:7.) In his opinion, there are multiple positive and negative regulatory loops operating in cells which, in the aggregate, create the results seen in experimental assays such as those conducted by Hoffman et al. Ravetch rejected the view that just one loop explains the activity of NF-κB in the cell. (Id. at 9:2-12.) The patent claims a reduction of NF-κB in cells, which Ravetch sees as encompassing the net effect of all events, both positive and negative,

which occur when a stimulus influences the cell. (Trial Tr. Day 3, 16:2-21.)

In addition, Ravetch testified that experiments using cells from knockout mice are conceptually flawed because they assume all other processes in the cell operate the same in the absence of the missing feature, an assumption he believes to be untrue. (Id. at 13:4-14.) Therefore, conclusions from these simplified models cannot be extrapolated back to normal cells because they do not take into consideration effects of the other components operating out of their normal context. (Id. at 13:21-14:4; see also id. at 30:19-32.) His opinion was that the scientific community has "established a model for the Autoregulatory Loop" to account for certain observations, but "there is considerable dispute and ongoing study to define its role in the NF-κB signaling pathway." (Id. at 42:9-21.) Ravetch also disputed that numerous scientific articles showed an acceptance by the scientific community of the existence and operation of the Autoregulatory Loop.[25] (See Trial Tr. Day 4, 55:7-70:3.) The articles, in his view, attempt to explain observations of experiments conducted with knockout mice, but the results are inconclusive because of the difficulties in interpreting signal transduction systems where the system has multiple interacting components. (Id. at 73:9-12; see also Trial Tr. Day 3, 32:11-21 (describing a paper in which the authors note their experimental observations are not consistent with the model proposed for the

[25] At the bench trial, I initially reserved judgment on whether the articles on which Dr. Ravetch was cross-examined were admissible. (See Trial Tr. Day 4, 55:6-9, 59:8-13.) In response, Lilly's attorney laid the foundation with the witness to admit the portions read into the record under the hearsay exception for learned treatises. Fed. R. Evid. 803(18) (allowing statements contained in scientific periodicals, established as a reliable authority by the testimony of an expert witness, to be read into evidence). Therefore, this portion of Ravetch's testimony is admitted.

Autoregulatory Loop); id. at 34:2-36:15 (discussing a paper suggesting that a more complex model is necessary to explain the processes occurring in living cells).) Ravetch noted that, far from there being a settled theory congruent with the experimental data, there is still significant ongoing research attempting to explain the complex phenomena taking place within the cell. (Trial Tr. Day 3, 23:4-7.)

Finally, Ravetch pointed out that the patent claims processes in living cells, while Latchman's opinion relied on in vitro research, such as the Hoffman paper (as described by Ting & Endy) to reach his conclusions concerning the Autoregulatory Loop. (See id. at 36:21-37:3.)

c. Cross-Examination of Dr. Latchman

On cross-examination, Latchman agreed that the experiments summarized by Ting & Endy were conducted in vitro on cell extractions, not in vivo. (Trial Tr. Day 1, 134:11-18, 140:2-7). He also acknowledged that at his deposition he described the results of their research as "a step along the road," but not determinative of how IκB-α works in the human body. (Id. at 148:8-23.) In addition, he admitted that there were discrepancies between the computer model of the Autoregulatory Loop proposed by Ting & Endy and the Hoffman empirical data. (Id. at 155:11-156:6.) Latchman also noted that the computer models of the Autoregulatory Loop are "continually being refined and [that] Hoffman [] published a paper as recently as two or three months ago in which he's changed the model again." (Id. at 156:6-10.)

d. There Is Insufficient Evidence to Invalidate the Patent

The '516 patent is "presumed valid." 35 U.S.C. § 282. In the instant case, Lilly

has the burden of proving facts by clear and convincing evidence showing that the patent is invalid. North Am. Vaccine v. American Cyanamid Co., 7 F.3d 1571, 1579 (Fed. Cir. 1993). Lilly has not met this burden.

While the evidence shows that there has been significant scientific research over more than a decade into the operation of the NF-κB signaling pathway, it has not established that the simplified model of the Autoregulatory Loop proffered by Latchman operates in vivo in normal cells. Latchman admits that, not only does the current model not fully explain the experimental data, but that the model is continually being refined, even to the present day. Scientists are conducting ongoing research to attempt to more fully explain what happens in cells when subjected to various external stimuli. Ravetch described a complex system of multiple feedback loops, all interacting, to effect the changes in gene expression claimed by the patent. In addition, the experimental data described in the literature has been collected using knockout cells in vitro that have not been shown to operate in all other respects as normal cells. The experimental data cannot be fully explained by the current model.

Therefore, I credit Dr. Ravetch's testimony that the Autoregulatory Loop is "an incomplete model . . . subject to a significant amount of ambiguity and inconsistency" (Trial Tr. Day 4, 50:2-6) and find that Lilly has failed to prove by clear and convincing evidence that the Autoregulatory Loop exists in living cells in a way that is encompassed by Ariad's claims.

B. Inequitable Conduct During Prosecution of the '516 Patent

Lilly asserts that Ariad, the inventors, and/or their attorneys failed to disclose to

the PTO material prior art that demonstrates inherent anticipation of the '516 patent and also failed to disclose material errors in a figure contained in the patent. Although I agree with Lilly that the information that was not disclosed is material, Lilly has failed to prove by clear and convincing evidence the requisite intent necessary to find inequitable conduct and render the patent unenforceable.

1. The Legal Standard for Inequitable Conduct

The patent application process is conducted ex parte by inventors and their representatives. Applicants have a duty to prosecute applications with candor, good faith, and honesty. Duro-Last, Inc. v. Custom Seal, Inc., 321 F.3d 1098, 1099 (Fed. Cir. 2003); see also 37 C.F.R. § 1.56 ("Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the [Patent] Office."). When coupled with an intent to deceive or mislead the PTO, a breach of this duty constitutes inequitable conduct, which renders the patent unenforceable. Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 326 F.3d 1226, 1233 (Fed. Cir. 2003). An applicant breaches this duty by making affirmative misrepresentations of material facts, failing to disclose material information, or submitting false material information. Duro-Last, 321 F.3d at 1099.

The Federal Circuit requires that a party asserting inequitable conduct show by "clear and convincing evidence" the elements of materiality and intent to deceive. Burlington Industries, Inc. v. Dayco Corp., 849 F.2d 1418, 1422 (Fed. Cir. 1988) (expressing concern about "the habit of charging inequitable conduct in almost every major patent case"). The analysis of inequitable conduct is a two-step process. First

the court must determine, as a threshold matter, if both the materiality of the information and the intent to deceive have been established. Bristol-Myers, 326 F.3d at 1234. Once the court has determined that the factual basis for materiality and intent exist, it must "weigh them to determine whether the equities warrant a conclusion that inequitable conduct occurred." Id. (quoting Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995)). This balancing means that a greater showing of one factor can compensate for a lesser showing of the other. Id.

a. Materiality

Information is material "where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow an application to issue as a patent." Digital Control, Inc. v. Charles Mach. Works, 437 F.3d 1309, 1315 (Fed. Cir. 2006) (citing 37 C.F.R. § 1.56 (1977)); accord Bristol-Myers, 326 F.3d at 1234; Molins, 48 F.3d at 1179 n.8. Under this standard, information can be material even though disclosure of it would not render the invention unpatentable. Digital Control, 437 F.3d at 1318. However, information that is merely cumulative or less pertinent than material considered by the examiner is not material in an inequitable conduct analysis. Molins, 48 F.3d at 1179.[26]

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[26] In 1992, the PTO revised 37 C.F.R. § 1.56 to create a narrower definition of materiality:

> [I]nformation is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
>
> > (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

b. Intent

That the withheld information is material, by itself, is inadequate to prove inequitable conduct. There must also be a showing that the information was withheld with an intent to deceive or mislead the PTO. Allen Organ Co. v. Kimball Int'l., Inc., 839 F.2d 1556 (Fed. Cir. 1988) ("[M]ateriality does not presume intent, which is a separate and essential component of inequitable conduct."). "Intent to deceive can not be inferred solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent." Hebert v. Lisle Corp., 99 F.3d 1109, 1116 (Fed. Cir. 1996). However, intent to deceive or mislead the PTO can rarely be shown by direct evidence, it is usually inferred from the facts. Bristol-Myers, 326 F.3d at 1239. "[T]he involved conduct, viewed in light of all the evidence, including evidence of good faith, must indicate sufficient culpability to require a finding of intent to deceive." Digital Control, 437 F.3d at 1319 (internal quotations and citations deleted). Mere error, even conduct that amounts to gross negligence, is not adequate to establish an intent to deceive. Molins, 48 F.3d at 1181. Where the alleged conduct is the nondisclosure of

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> (2) It refutes, or is inconsistent with, a position the applicant takes in:
> (i) Opposing an argument of unpatentability relied on by the Office, or
> (ii) Asserting an argument of patentability.

37 C.F.R. § 1.56(b) (1992). Until recently, it was unclear if the Federal Circuit intended the PTO's 1992 updated definition of materiality to supplant existing case law. See, e.g., Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Inc., 394 F.3d 1348, 1353 (Fed. Cir. 2005) (applying the amended Rule 56 where the patent was prosecuted after the effective date of the rule change); Purdue Pharma L.P. v. Endo Pharm. Inc., 438 F.3d 1123, 1129 (Fed. Cir. 2006) (same). In Digital Control, however, the court made it clear that the 1992 revision did not replace the "reasonable examiner" standard, rather it supplemented it. Digital Control, 437 F.3d at 1316. The Federal Circuit explained that the new Rule 56 standard provides an additional test for materiality. Id.

information, there must be clear and convincing evidence that the applicant made a deliberate decision to withhold the information from the PTO. Id.

2. The Allegedly Withheld Information

According to Lilly, two errors made during prosecution of the '516 patent meet the threshold standard for materiality: (1) information that was incorrect was not provided to the PTO; and (2) references relevant to inherent anticipation of the claims were not disclosed.[27]

a. Errors in Figure 43

First, Lilly points to figure 43, three pages depicting a lengthy nucleotide sequence consisting of the letters A, C, G and T. The central portion of the sequence has sequential groups of these letters identified by an additional single letter below each group of three representing the amino acid sequence. ('516 Patent fig.43.) The Brief Description of the Drawings describes this figure as "the nucleotide sequence and the amino acid sequence of IκB-α." (Id. col.10 ll.16-17.) The only reference in the specification to figure 43 states: "The nucleotide sequence of the IκB-α gene and the amino acid sequence of IκB-α are shown in FIG. 43." (Id. col.28 ll.16-17.) Lilly argues that one skilled in the art reading the patent would expect figure 43 to describe the DNA and amino acid sequence for mammalian, specifically murine (mouse), IκB-α.

[27] An invention is patentable only if no relevant prior art contains all of the claimed elements. If all of the claimed elements are disclosed in a single reference, that prior art expressly anticipates the invention. If particular elements are missing but necessarily present in the prior art, that reference inherently anticipates the invention. Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1375 (Fed. Cir. 2005); see also Herbert Schwartz, Patent Law and Practice § 4.I.C.1. (5th ed. 2006).

However, figure 43 actually shows the sequence of an avian (chicken) protein called pp40. In addition, Lilly claims that the figure is incomplete and only shows portions of the amino acid sequence of pp40. Ariad counters that pp40 is an IκB-α protein, therefore there is no error in the identification of the figure, much less a material misrepresentation. As discussed below, I agree with Lilly that the fact that figure 43 does not represent mammalian DNA meets the threshold standard of materiality necessary to proceed with an evaluation of inequitable conduct. In addition, I find that the sequence in the figure is indeed incomplete as alleged by Lilly.

b. References Showing Inherent Anticipation

Second, Lilly avers that Ariad failed to disclose references relevant to inherent anticipation of the claims in the '516 patent. Specifically, Lilly argues that after the patent application was filed, at least one of the inventors published both a review article and a paper describing a number of prior art compounds as inhibitors of NF-κB activity. Lilly claims that Ariad had a duty to disclose this information to the PTO. It points to the results of the recent reexamination of the '516 patent, in which the PTO invalidated the claims at least partially on a determination that the claims were inherently anticipated by these references, as showing the materiality of the information withheld. Because I do not find the information withheld was merely cumulative, as Ariad suggests, I conclude it is material.

3. The Materiality of the Errors and Omissions in Figure 43

a. The Description of Figure 43 Is Incorrect

Ariad does not dispute that figure 43 represents the nucleotide sequence of avian pp40, not mammalian IκB-α. (See Docket # 398 ¶ 275.) However, it insists that describing pp40 in figure 43 as "the IκB-α gene" is neither incorrect nor misleading and therefore cannot support a claim of inequitable conduct. This conclusion is based on Ariad's assertion that "the term IκB-α refers to a family of proteins" capable of inhibiting NF-κB and that "the scientific community has reached a consensus that pp40 is an IκB-α protein." (Id. ¶¶ 262, 256.) Ariad further argues that the depiction of avian pp40 in figure 43 is not misleading because the methods claimed in the '516 patent are not limited to mammalian cells.[28] It points to text in the '516 specification explicitly describing the use of pp40, along with mammalian MAD-3, as potential sources for DNA used to negatively regulate NF-κB activity in cells (and thus practice the patented method) in support of this argument. ('516 Patent col.32 ll.11-40.)

Ariad's argument is disingenuous. While the '516 claims do broadly cover both mammalian and non-mammalian cells, the specification describes the inventors' work using a mammalian cell line. ('516 Patent col.22 l.23 - col.28 l.18.) The Detailed

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[28] This assertion is correct. Under the doctrine of claim differentiation the '516 claims must encompasses avian and other non-mammalian cells. See Phillips v. AWH Corp., 415 F.3d 1303, 1315 (Fed. Cir. 2005) "[T]he presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim."). Compare, e.g., '516 Patent claim 9 ("A method for modifying effects of external influences on a eucaryotic cell [characteristic of all life forms except primitive microorganisms] . . ."), with id. claim 94 ("The method of claim 9, carried out on mammalian cells.").

Description of the Invention leading up to the only paragraph referencing figure 43 begins, “[t]he following is a description of the . . . discovery of the NF-κB inhibitor IκB . . .” (Id. col.10 ll.46-52). What then follows is a lengthy discussion of the discovery and isolation of IκB-α from a murine cell line called 70Z/3. (Id. col.22 l.23 - col.28 l.18.) The sole mention of figure 43 (describing it as “IκB-α”) occurs in the text directly following a sentence describing how the inventors determined the characteristics of the IκB they isolated from this murine cell line. (Id. col.28 ll.14-18.) The obvious conclusion is that both sentences refer to the same protein.

One column later, the patent explicitly refers to “IκB prepared from the mouse [] cell line . . . .” (Id. col.29 ll.33-34.) A page later, the specification states: “[as] a result of the work described herein, the IκB gene is now available . . . ." (Id. col.31 ll.57-58 (emphasis added).) Latchman testified that in November 1991 when the application containing figure 43 was filed, pp40 was characterized as “an IκB-α like molecule.” It was not until several years later that pp40 was referred to simply as IκB-α. (Trial Tr. Day 1, 98:7-99:16.) Furthermore, while the terms “human,” “mammalian,” “murine,” “mouse,” and “70Z/3" occur throughout the specification, “avian” and “chicken” do not appear at all, and “pp40" appears only once. Based on these facts, I find that a reasonable examiner would believe the sequence depicted in figure 43 to represent the nucleotide sequence and the amino acid sequence of murine IκB-α, not avian pp40.

b. Figure 43 Is Incomplete

Latchman also testified that figure 43 is incomplete and does not show the correct full amino acid sequence even of pp40. In particular, he stated that figure 43

shows an amino acid sequence that has 82 amino acids at the beginning of the figure that are not present in pp40, but it is missing 56 amino acids at the end, for which are substituted 10 amino acids that are not present in pp40. (Id. at 106:4-20.) The missing region corresponds to a portion of IκB-α necessary to inhibit DNA binding of NF-κB. (Id.) Based on a comparison of figure 43 with the published sequence of pp40, I credit Latchman's testimony.[29] Because there is no evidence that Ariad was aware of this error while prosecuting the '516 patent, the error does not affect the issue of intent in evaluating inequitable conduct. See M. Eagles Tool Warehouse, Inc. v. Fisher Tooling Co., 439 F.3d 1335, 1341 (Fed. Cir. 2006) ("In an inequitable conduct determination based upon a nondisclosure, the applicant must know, or should have known, of the materiality of the reference for an inference of intent."). However, it does increase the

[29] During the bench trial, Ariad moved to strike Latchman's testimony concerning the error in figure 43, arguing it was not previously disclosed in his expert report. (Trial Tr. Day 1, 106:21-22.) However, in its proposed findings of fact, Ariad did not contest his conclusions nor did it claim that figure 43 is correct, rather it attacked Latchman's credibility for failing to recognize this error previously and recommended that the court "find that Figure 43 corresponds to pp40 as Latchman originally testified." (Docket # 398 ¶¶ 273-75.) Ariad further asserts that "[t]here is no way to authenticate Latchman's analysis [comparing the sequences in figure 43 to the identical sequence presented in the Davis (1991) journal article]." (Id. ¶¶ 281-82.) However, in a separate section of its proposed findings, arguing that the information concerning figure 43 was merely cumulative, Ariad suggests that "[having] copies of [] Davis (1991) . . . , the patent examiner responsible for the examination of the '516 patent had available to him all the relevant information necessary to compare the sequences in figure 43 with the sequences disclosed for pp40 in Davis . . . ." (Id. ¶ 251.) Taking Ariad up on its offer, the court compared the amino acid sequences shown in figure 43 and Davis (1991), Fig. 3., and finds that Latchman's testimony accurately described figure 43 as not showing the correct amino acid sequence of pp40. Having performed this tedious comparison, the court further credits Latchman's testimony that a skilled reader would not have checked the sequences in figure 43 against the published references. (Trial Tr. Day 1, 105:14-15.)

materiality of the error, because it means that the amino acid sequence shown cannot be used as described in the '516 patent to reduce the activity of NF-κB.

c. Figure 43 Is Material Despite Its Late Addition to the Application

Ariad suggests that since figure 43 was added to the application in 1991, after the 1989 filing date established by the jury, it is not necessary to the invention and therefore cannot be material, even if wrong. This argument fails under either standard for materiality. Under the "reasonable examiner" standard, the information does not have to preclude patentability to be material. E.g., Digital Control, 437 F.3d at 1318; Bristol-Myers, 326 F.3d at 1237. Even under the stricter standard promulgated by the PTO in 1992, information that "is inconsistent with, a position the applicant takes in: . . . (ii) Asserting an argument of patentability" is material. 37 C.F.R. § 1.56(b) (1992). As discussed infra, p. 30, Ariad responded to a PTO section 112 rejection by pointing to the disclosure of IκB-α as enabling of its claims, thus "asserting an argument of patentability." Therefore, the error is material regardless of the patent filing date.[30]

[30] In addition, the standards of proof to establish the filing date differ between patent prosecution and a jury trial on validity. At trial, the patent '516 was presumed valid and the defendant had the burden to show invalidity by "clear and convincing evidence." E.g., Oakley, Inc. v. Sunglass Hut Int'l, 316 F.3d 1331, 1339 (Fed. Cir. 2003); 35 U.S.C. § 282 (2002). During prosecution, however, the examiner uses a preponderance of the evidence standard, and in some cases the burden is shifted to the applicant to prove the claims are patentable. See 37 C.F.R. § 1.56 (2006) (describing preponderance of the evidence as the standard to evaluate unpatentability in determining materiality); Manual of Patent Examining Procedure ("MPEP") § 2112(V.) (shifting the burden of proof to applicant after an inherency rejection under 35 U.S.C. § 102 or a "prima facie obviousness" rejection under 35 U.S.C. § 103); see also (Office Action in Ex Parte Reexamination, Patent 6410516, August 2, 2006 (DTX 973A) at 8) ("[T]he existence of a final court decision of claim validity in view of the same or different prior art does not necessarily mean that no new question is present, because of the different standards of proof employed by the Federal District Courts and the

d. Figure 43 Is Not Cumulative

Finally, Ariad's argument that any disclosure of the error in figure 43 was merely cumulative, because the examiner could have compared the sequence in the patent application with Davis (1991), Fig. 3, is unpersuasive. (Plaintiffs' Trial Exhibit ("PTX") 143.)[31] Indeed, as discussed supra, note 29, I find it unreasonable to expect the examiner to compare the sequences. In any case, since figure 43 is not identical to the figure showing pp40 in Davis, even if the examiner had compared the sequences he would not necessarily have realized that figure 43 was an incorrect sequence of pp40 and not the sequence of murine IκB. Id.

Ariad also suggests the information is cumulative because one of the examiners of the '516 patent, Dr. Schwartzman, was also the primary examiner of the application that issued as the '090 patent. (Docket # 398 ¶ 239-40.) It notified Dr. Schwartzman during the prosecution of the '090 patent that an identical figure in the '090 application was "not the nucleotide sequence of IκB-α but the nucleotide sequence of pp40 rel-associated protein." (Id.) Presumably, Ariad believes that the examiner should sua sponte have applied this information to the examination of the '516 patent as well. The duty of candor and good faith exists to ensure that patent applicants provide accurate material information to the PTO so that the examiner can efficiently and effectively assess their claims. The duty of candor is not so lax that it requires an examiner to

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Office.").

[31] Nathan Davis, et al., Rel-Associated pp40: An Inhibitor of the Rel Family of Transcription Factors, 253 Science 1268, 1270 (1991).

compare nucleotide sequences or to track what figures are shared between divisional applications. See also Armour & Co. v. Swift & Co., 466 F.2d 767, 779 (7th Cir. 1972) ("[W]e think that it is unfair to a busy Examiner . . . to assume that he retains details of every pending file in his mind when he is reviewing a particular application."). Therefore, I decline to find that information concerning the errors in figure 43 is merely cumulative on that basis.

e. The Errors in Figure 43 Are Material Under Both Standards

To determine the materiality of the error in figure 43, it is necessary to consider what information the examiner relied on in examining the '516 application during its prosecution. The prosecution history shows that the examiner expressed concern on multiple occasions that the '516 application either did not satisfy the written description requirement or was not enabled. (See, e.g., DTX 2 at ADL611-21, ADL613 (March 11, 1999 PTO Office Action rejecting twenty claims as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art . . . to make and/or use the invention."); id. at ADL478-88, ADL480 (October 1997 Office Action rejecting claims for lack of enablement and written description); id. at ADL447-55, ADL450-35 (January 1997 Office Action rejecting claims for lack of enablement); id. at ADL822-33, ADL824-25.) In a July 1998 Office Action, the examiner rejected several claims because the specification failed to teach how to purify either the NF-κB or IκB protein. Ariad responded that "the present application teaches how to make recombinant forms of the proteins." (Id. at ADL570-88, ADL585.) In response to the October 1997 Office Action, the applicants argued that there was adequate disclosure

to support, inter alia, that the "artificial induction of IκB could be used as a means of inhibiting NF-κB activities as its regulation of gene transcription." (Id. at ADL517-40, ADL529.)

These rejections and Ariad's responses show that the DNA sequence of IκB-α was material because Ariad asserted in an argument for patentability that it taught how to make the protein and thus enabled their claims. The correct sequence information was also necessary in order to incorporate IκB-encoding DNA into the appropriate vector for gene therapy as described by the '516 patent. ('516 Patent col.32 ll.12-63.) While pp40 is an inhibitor of NF-κB in chickens, it is not clear that it operates similarly in mammals. (Trial Tr. Day 1, 123:2-5.) Latchman testified that in order to have the greatest chance for success in human gene therapy, it is important "to have as much going for you as possible." (Id. at 101:14-23.) In particular, he warned that using a gene from a non-mammalian species is "more likely to raise an immune reaction and the protein is likely to have functional differences." (Id.) Thus, the information that the sequence showed avian pp40 and therefore was less likely to enable the claimed method without undue experimentation, would have been of interest to a reasonable examiner, particularly here where enablement was an issue. Cf. Regents of Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1567 (Fed. Cir. 1997) (finding the disclosure of rat cDNA inadequate to fulfill the written disclosure requirement of a patent claiming human insulin-encoding cDNA). Finally, even if I accept Ariad's claim that pp40 is an IκB and thus could be used to make or use the invention, the sequence in figure 43 is not the correct sequence of pp40 as shown in Davis (1991). (PTX 143.) For these

reasons, I find that the error in figure 43 is material.

4. The Materiality of the Prior Art References

Lilly also alleges that Ariad intentionally withheld certain references from the PTO during prosecution of the '516 patent that were material to the question of inherent anticipation. "A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention." Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003). Even if a limitation of the claimed invention is missing in the prior art reference, the patent may still be anticipated if "the missing characteristic is necessarily present, or inherent, in the single anticipating reference." Id. Lilly points to several post-filing references related to the effects on NF-κB activity of various compounds known before the filing date of the patent that it believes should have been provided to the PTO. Specifically, it cites several articles by co-inventor Baldwin, including:

> Baldwin, A.S., The NF-κB and IκB Proteins: New Discoveries and Insights, Annu. Rev. Immunol. 14:649-81 (1996) (DTX 24-S);
>
> Baldwin, A.S., The Transcription Factor NF-κB and Human Disease, J. Clinical Investigation 107(1):3-6 (2001) (DTX 25);
>
> Scheinman et al., Role of Transcriptional Activation of IκB-α in Mediation of Immunosuppression by Glucocomcoids, Science 270:283-286 (1995) (DTX 28); and
>
> Holmes-McNary, M. and Baldwin, A.S., Chemoprotective Properties of trans-Resveratrol Are Associated with Inhibition of Activation of the IκB Kinase, J. Cancer Research 60:3477-3483 (2000) (DTX 473),

("the Baldwin references") as well as the relevant references cited in them as disclosing that glucocorticoids, salicylates, cyclosporin A, and resveratrol (Res) – an active

ingredient in red wine – all inhibit NF-κB activity. (DTX 24-S at 671; DTX 25 at 4; DTX 28 at 283; DTX 473 at 3481-82.) When these references were brought to the PTO's attention in the reexamination proceedings, the PTO invalidated the claims at issue in this case as being inherently anticipated. (Office Action in Ex Parte Reexamination, Patent 6410516, August 2, 2006 (DTX 973A).) Lilly argues this demonstrates under both the "reasonable examiner" and stricter "prima facie case of unpatentability" standards that the references were material. See Molins, 48 F.3d at 1179 (noting that "the result of a PTO proceeding that assesses patentability in light of information not originally disclosed can be of strong probative value in determining whether the undisclosed information was material").

Ariad's counters that these references: (1) were not material because they were cumulative to material already provided to the examiner; and (2) even if they were not cumulative, they were not material because the law at the time included a contemporaneous recognition requirement that one of ordinary skill would have had to recognize the missing information inherently disclosed.[32]

a. The Cited References Are Not Cumulative

First, Ariad points to a 1994 paper by Ulrich Siebenlist ("Siebenlist 1994") (DTX 2 at ADL649-73)[33] provided to the PTO as an exhibit to a declaration (id. at ADL625-

[32] Ariad also argues that the references cannot be material because the jury found they do not make the asserted claims unpatentable. (Docket # 398 ¶ 48.) As discussed supra p. 21, the standards for materiality do not preclude information from being material even if the claims are ultimately found to be valid.

[33] Siebenlist et al., Structure, Regulation and Function of NF-κB, 10 Ann. Rev. Cell. Biol. 405-55 (1994).

27) by one of the inventors of the '516 patent, Dr. Baltimore. This first declaration was submitted in support of Ariad's response to a March 17, 1999 PTO Final Office Action rejecting all pending claims for failing to satisfy the enablement requirement of 35 U.S.C. § 112. (See id. at ADL610-21, ADL613; ADL697-704, ADL700.) The copy of the first Baltimore declaration in the PTO prosecution history contains the handwritten notation, "Considered 11/19/99," followed by Examiner Schwartzman's initials.[34]

Siebenlist 1994 includes brief discussions relevant to inherent anticipation including: (1) that cyclosporin A blocks activation of NF-κB (citing Schmidt et al. 1990) (id. at ADL661); and (2) that the actions of steroids, including glucocorticoids, could be explained by their complexing with NF-κB (citing Ray & Perfontaine 1994) (id. at ADL664). While Siebenlist 1994 does not mention resveratrol specifically, it does discuss the inhibition of NF-κB activation by antioxidants. (Id. at ADL659.) Ariad argues this is an adequate disclosure of resveratrol because it is an antioxidant.

Next, Ariad points to the response to an August 11, 2000 Office Action that it sent to Examiner Schwartzman on September 12, 2001. (Id. at ADL872-92.) Again, Ariad included a declaration by inventor Baltimore along with 100 pages of attached references. Baltimore described several classes of compounds that "are able to affect

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[34] The initials are indecipherable, however they appear similar to those of the examiner who initialed the '516 patent search history. (See DTX 2 at ADL4.) Furthermore, the notation on the first Baltimore declaration was dated the same day Examiner Schwartzman signed an Office Action responding to the arguments made in the Ariad September 21, 1999, response that included the declaration. (See DTX 2 at ADL707-16, ADL716.) Finally, Matthew Vincent, the patent attorney for Ariad prosecuting the '516 patent, testified that he recognized the initials as those of Examiner Schwartzman. (Trial Tr. Day 3, 53:18-25.) Based on this evidence, I find that the initials on the first Baltimore declaration are Schwartzman's.

NF-κB gene expression" including salicylates (citing, but not providing, a 1999 paper by Yan et al.).[35] (Id. at ADL894-97, ADL895-96.) This response included a copy of a 2000 paper by Fujihara ("Fujihara 2000")[36] citing an number of NF-κB inhibitors previously described including glucocorticoids, aspirin and antioxidants. (Id. at ADL904-12, ADL904.)

Less than a month later, on October 4th, Examiner Guzo allowed the amended claims noting that he "ha[d] reviewed the last response and accompanying references which provide substantiating examples of the claimed methods." (Id. at ADL923-53, ADL952.) Ariad asserts that this language indicates that the examiner considered the post-filing references, including Fujihara 2000, and was aware of the 1999 Yan paper. Because these references, taken together, disclose use of the same prior art compounds as the references advanced by Lilly, Ariad argues that the withheld references are merely cumulative, and thus cannot be material.

Lilly's response is that the Baltimore declarations and accompanying references were provided only to contest claim rejections based on the written description and enablement requirements. While the PTO did accept the references submitted in support of the applicant's response to the Office Action without an Information

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[35] Yan et al., Aminosalicylic Acid Inhibits IκB Kinase α Phosphorylation of IκBα in Mouse Intestinal Epithelial Cells, 274 J. Biol. Chem. 36631 (1999).

[36] Fujihara et al., A D-Amino Acid Peptide Inhibitor of NF-κB Nuclear Localization is Efficacious in Models of Inflammatory Disease, 165 J. Immunol. 1004 (2000).

Disclosure Statement ("IDS"), the Manual of Patent Examining Procedure ("MPEP")[37] at the time implied that the references would only be reviewed for the specific issue being advocated.[38] In addition, Ariad's response to the Office Action only discussed why the provided references were relevant to the adequacy of the '516 disclosure, not to inherent anticipation. Ariad's patent attorney for the '516 application, Dr. Matthew Vincent ("Vincent"), confirmed that Ariad did not read the publications at the time "with any appreciation that someone might argue that they were relevant to inherent

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[37] "The MPEP is commonly relied upon as a guide to patent attorneys and patent examiners on procedural matters. While the MPEP does not have the force of law, it is entitled to judicial notice as an official interpretation of statutes or regulations as long as it is not in conflict therewith." Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 n.10 (Fed. Cir. 1995) (internal citations and quotations marks omitted).

[38] References normally must be submitted with an IDS to be considered by the PTO. See 37 C.F.R §§ 1.97, 1.98. The MPEP at the time of the '516 prosecution provided an exception for references submitted with an Office Action response, in pertinent part as follows:

> To the extent that a document is submitted as evidence directed to an issue of patentability raised in an Office action, and the evidence is timely presented, applicant need not satisfy the requirements of 37 CFR 1.97 and 37 CFR 1.98 in order to have the examiner consider the information contained in the document relied on by applicant. In other words, compliance with the information disclosure rules is not a threshold requirement to have information considered when submitted by applicant to support an argument being made in a reply to an Office action.

MPEP § 609 C (3) (7th ed. July 1998) (emphasis added). The next edition of the MPEP added a sentence to this exception to make it clear that the PTO only considered the reference for the issue proffered. MPEP § 609.05(c) (8th ed., rev. 5, Aug. 2006) ("[C]onsideration by the examiner of the document submitted as evidence directed to an issue of patentability raised in the Office action is limited to the portion of the document relied upon as rebuttal evidence; the entirety of the document may not necessarily be considered by the examiner.").

anticipation." (Trial Tr. Day 3, 107:25-108:4.) The PTO Notice of Allowability notes that the examiner amendments to the claims proposed by Ariad were authorized in a telephone interview with Vincent on September 14, 2001, only two days after the examiner received the 100-page document. (DTX 2 at ADL924.) Mr. Lieberstien, Lilly's patent expert, testified that this kind of examiner's amendment normally means allowance of the claims. (Trial Tr. Day 2, 105:12-17.) Lilly further notes that the sections of Siebenlist 1994 relevant to inherent anticipation are twenty pages removed from the sections Ariad drew to the attention of the examiner in the first Baltimore declaration. It points out that there is no evidence in the prosecution history that the examiner was aware of the information in Siebenlist 1994 and Fujihara 2000 describing prior art compounds. Finally, none of these references specifically mentions the use of resveratrol or red wine; rather they only discuss the more general use of antioxidants to inhibit NF-κB activity.

Given the limited purpose for which the references were proffered, the fact that they were not listed in an IDS, the exceedingly short time between the receipt of the second Baltimore declaration and the examiner's amendments suggesting allowance, and the lack of specific reference to resveratrol or red wine, I do not find that the Baltimore declarations and attachments adequately disclosed the prior art compounds described in the Baldwin references. Therefore, the Baldwin references are not merely cumulative and thus may be material in an analysis of inequitable conduct.

b. Recognition Requirement for Inherent Anticipation

Even if the Baldwin references are not merely cumulative, Ariad insists that a

reasonable examiner would not have considered them material because at the time the PTO had a recognition requirement for inherent anticipation. Under this doctrine, a reference does not inherently anticipate an invention unless it both necessarily includes the missing element and that missing element would be recognized as necessarily included by a person of ordinary skill at the time. In support of its position, Ariad points to instructions to the examiner on inherent anticipation in the edition of the MPEP in effect at the time of the '516 prosecution:

> To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

MPEP § 2112 (7th ed. July 1998) (citing In re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999) (internal quotations omitted). Ariad contrasts this language with the subsequent edition of the MPEP, which explicitly states that contemporaneous recognition is not a requirement for inherent anticipation.[39] It argues that this shows that a change in the PTO's position on inherent anticipation occurred after the prosecution of the '516 patent which eliminated the recognition requirement. (See Docket # 398 ¶¶ 121-124.)

The difficulty with this argument is that the 7th edition of the MPEP did not require contemporaneous recognition, only an ultimate recognition of the inherency, and it is not in conflict with the additional guidance provided in the later edition.

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[39] See MPEP § 2112 (II.) (8th ed., rev. 5, Aug. 2006) ("There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference.") (emphasis in original) (citing Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003)).

Moreover, with one exception, the cases relied upon by Ariad, while requiring recognition by persons of ordinary skill, are silent as to whether that recognition must be contemporaneous with the date of the reference. See Robertson, 169 F.3d at 745. ("the extrinsic evidence must make clear that the missing descriptive matter . . . would be so recognized by persons of ordinary skill") (internal quotations removed); Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268, (Fed. Cir. 1991) (same); Electro Med. Sys., S.A. v. Cooper Life Sciences, Inc., 34 F.3d 1048, 1052 (Fed. Cir. 1994) ("EMS was required to prove . . . and that it would be so recognized by persons of ordinary skill."). The sole exception that explicitly required contemporaneous recognition is Elan. Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research, 304 F.3d 1221 (Fed. Cir. 2002) ("[I]t must be shown that the undisclosed information was known to be present in the subject matter of the reference."), vacated 314 F.3d 1299 (Fed. Cir. 2002), and superceded 346 F.3d 1051 (Fed. Cir. 2003). However, that decision was vacated and the new decision does not contain a similar requirement. (Id.) Also, as Lilly points out, Elan was decided after the '516 patent issued, so it could not have been considered by the examiner as a statement of the law at the time of the '516 prosecution. I note that Schering, the case cited in the 8th edition of the MPEP, explicitly rejected both the holding in Elan and Ariad's reading of Continental Can as requiring contemporaneous recognition. Schering, 339 F.3d at 1377.

In addition, the examiner of the '516 patent continued to reject a claim even after Ariad argued that there was no contemporaneous recognition in the reference to support the examiners inherent anticipation rejection. In that instance, Ariad asserted

that the reference Wall et al. could not be prior art because it did not "teach or suggest that NF-κB is a trans-acting nuclear factor, nor do they teach or suggest that NF-κB binds to the enhancer of the κ gene." (DTX 2 at ADL470-71.) The examiner, in maintaining the rejection, stated that "[a]lthough these references do not teach the NF-κB--IκB-α complex, the role of NF-κB as a transcription factor or the presence of NF-κB binding sites in the expressed genes, these are inherent properties of the cells and the genes." (DTX 2 at ADL486.) This indicates that the examiner of the '516 patent did not accept Ariad's argument that there was a contemporaneous recognition requirement for inherent anticipation. Thus, the case law and the '516 examiner's actions support Lilly's position that a reasonable examiner would not reject references describing use of the prior art compounds because of a lack of contemporaneous recognition of their mode of action.

I therefore find that the Baldwin references are material because: (1) they disclose references pertaining to prior art compounds that the examiners, on reexamination, found were material to the issue of patentability; (2) they are not cumulative to references provided during the prosecution of the '516 patent, and; (3) a reasonable examiner, at the time of the prosecution of the '516 patent, would not have believed there was a contemporaneous recognition requirement for inherent anticipation.

5. Evidence of Intent Concerning the Errors in Figure 43

Lilly argues that Ariad's patent attorneys were not only aware that figure 43 was not the sequence of IκB-α as described, but also that the information was material to

the asserted claims. In addition, Lilly suggests that Ariad had a strong motivation to conceal this information because disclosure might have required Ariad to refile the application and lose the benefit of the transitional rules. Without the benefit of the transitional rules, the patent would have expired on January 9, 2006, twenty years from its original filing date, rather than seventeen years from issuance, in 2019. Lilly asserts that the failure to inform the PTO of the error, coupled with the desire to secure an additional thirteen years of patent monopoly, provides adequate circumstantial evidence of an intent to conceal material information and justify a finding of inequitable conduct. (See Docket # 397 ¶¶ FF110-18.)

a. The Prosecuting Firm and Attorney History of the '516 Patent

The complexity of the prosecuting attorney history of the '516 patent rivals that of its PTO prosecution history. Figure 43, identified as "the nucleotide sequence and the amino acid sequence of IκB-α," was added as new matter in application 07/791,898, a continuation-in-part of several earlier Ariad applications, filed November 13, 1991. (DTX 33 at ADL14822, 14851.) This application was eventually abandoned, but not before a continuation application, 08/418,266 ("the '266 application"), also containing figure 43 was filed on April 6, 1995. The '266 application spawned two divisional applications containing figure 43, 08/463,397 ("the '397 application") and 08/464,364, which issued as the '516 patent.[40] (See DTX 3300 (demonstrative exhibit

[40] A divisional application is a type of continuation patent application. An applicant is only allowed to claim one invention in a patent. If the PTO determines that an application contains more than one invention, it issues a restriction requirement and the applicant must either abandon all but one invention or create one or more divisional applications to pursue the other inventions in separate applications. See generally

showing the '516 patent family lineage).) The '266 application eventually issued as U.S. Patent No. 5,804,374 on September 8, 1998. After the claims were allowed, but before the patent issued, figure 43 was deleted from the '266 application. At that time the applications were being prosecuted by the firm of Hamilton, Brooks, Smith & Reynolds, P.C. Lisa Warren ("Warren"), an attorney associated with that firm, filed an amendment with the PTO on September 15, 1997, to remove figure 43 and more than 30 other figures. (DTX 34 at ADL15351-71.) Warren explained in the amendment that the applicants did not believe the deleted figures were necessary for an understanding of the invention. (Id. at 15370.) However, she also noted that "[i]t has recently come to the Applicants' Attorneys' attention that figure 43 is not the nucleotide sequence of IκB-α but the nucleotide sequence of pp40 rel-associated protein." (Id.) This information apparently had been provided by Ariad employee Sharon Hausdorff ("Hausdorff"). (See Clauss Dep. Tr., 44:18-22, 62:2-6.) The PTO subsequently disapproved the request to amend due to confusion over the adequacy of the amendment. (DTX 34 at ADL15341.)

In late 1997, after this amendment was filed, but before it had been denied by the PTO, responsibility for prosecution of the outstanding applications was transferred to the firm of Foley, Hoag & Elliot LLP ("Foley Hoag"). (Id. at ADL15373.) Dr. Isabelle Clauss ("Clauss") was responsible for the day-to-day work on the applications. However, Clauss had only limited recognition to prosecute patents for others before the

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Herbert Schwartz, Patent Law and Practice § 2.III.D.6.c. (5th ed. 2006).

PTO.[41] She worked with Vincent, who was the attorney at Foley Hoag responsible for the overall strategy for the prosecution of the Ariad applications. (Trial Tr. Day 3, 44:16-25, 89:13-25.) Vincent, an associate only three years her senior, testified that he provided guidance to Clauss and reviewed "substantive papers" she submitted to the PTO, as well as any other paper she brought to his attention. (Id. at 90:19-23.) However, Clauss would have handled "ministerial" actions, such as resubmitting documents, responding to requests for references and some amendments, on her own. (Id. at 91:2-12). On March 6, 1998, Clauss re-filed the previously disapproved amendment signed by Warren cancelling, inter alia, figure 43 and containing the admission that "Figure 43 is not the nucleotide sequence of IκB-α." (DTX 34 at ADL15343-44.) The PTO approved the resubmitted amendment and the patent on the '266 application issued without figure 43.

On January 12, 2000, after the claims were allowed on the divisional '397 application but before issuance, Clauss filed an amendment to delete the same figures that had been deleted in the '266 application, including figure 43. The statement "[i]t has recently come to the Applicants' Attorneys' attention that figure 43 is not the nucleotide sequence of IκB-α but the nucleotide sequence of pp40 rel-associated protein" appeared on the last page of the amendment, the same page bearing Clauss' signature. (DTX 131 at ADL3629.) Again, this information apparently had been provided by Ariad's Hausdorff. (See Clauss Dep. Tr., 44:18-22.) The PTO approved

[41] Clauss was granted limited recognition as a resident alien to prepare and prosecute patent applications under 37 C.F.R. § 10.9(b). (See DTX 34 at ADL15345.)

the amendment and this patent also issued without figure 43.

In the beginning of 2001, Vincent moved his practice from Foley Hoag to Ropes & Gray LLP. The outstanding Ariad applications were transferred about the same time. (Trial Tr. Day 3, 44:1-6, 46:16-24.) Clauss remained at Foley Hoag and did no further work on any Ariad patent applications. The '516 patent ultimately issued on June 25, 2002. Lilly argues that the failure of Hausdorff, Vincent and Clauss to disclose the error in figure 43 to the PTO meets the threshold standard for intent necessary to consider a claim of inequitable conduct.

b. Evidence of Intent by Hausdorff

Lilly's allegations fail as to Hausdorff. Hausdorff clearly was aware of the error, since she provided the information that figure 43 was incorrect in the '266 and '397 applications to the prosecuting attorneys. However, absent any showing that she intended the same information to be withheld on the '516 application, I cannot find an intent to mislead. It is troubling that PTO records show Hausdorff accompanied Vincent on two in-person interviews with Examiner Schwartzman during the prosecution of the '516 patent and after the figure had been removed from the other two patents. (See Interview Summary, April 7, 1998 (DTX2 at ADL495); Interview Summary, Jan. 26, 1999 (id. at ADL609).) However, Vincent's testimony did not establish that issues relevant to the figure were discussed or that Hausdorff intentionally withheld information. (Trial Tr. Day 3, 48:10-24.) She had previously disclosed the error to Clauss (who was not present at either PTO interview). As the representative of the client, she may have expected the patent attorneys at Foley Hoag to determine what

information was relevant to discuss with the examiner.[42]

c. Evidence of Intent by Vincent

Lilly's allegations against Vincent rest solely on the deposition testimony of Clauss.[43] Clauss, not Vincent, signed both the '266 amendment resubmittal and the '397 amendment, each of which admitted the error in the figure. Vincent testified that neither Clauss nor anyone else indicated to him that there was an issue with figure 43 during the pendency of the application for the '516 patent. (Trial Tr. Day 3, 64:25-65:3.) This is in conflict with Clauss' testimony, in which she stated that she discussed the issue regarding figure 43 with him.[44] (See Clauss Dep. Tr., 57:18-22.) However, I find his testimony credible and therefore conclude that he did not conceal the error in figure 43, intentionally or otherwise.

d. Evidence of Intent by Clauss

Lilly's strongest evidence of misconduct is Clauss' failure to inform the PTO of the error in figure 43, but ultimately this too fails to rise to clear and convincing proof of

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[42] In its proposed findings of facts, Lilly describes Hausdorff as "a patent agent at Ariad," however, it fails to cite to evidence in support of this description. (Docket # 397 ¶ FF119.) Even assuming she was a registered patent agent, there is still insufficient evidence to conclude that Hausdorff intentionally withheld the information concerning figure 43 from the PTO.

[43] Dr. Clauss did not testify at the bench trial; only a copy of her deposition testimony was available to the court.

[44] Clauss' testimony on the issue is, at best, equivocal. She was uncertain about the time the conversations took place (Clauss Dep. Tr., 58:1-12), which patent applications they related to (id. at 58:13-19), whether the discussions included figure 43 being in error (id. at 68:5-19) or whether Vincent had seen the resubmittal to the PTO. (Id. at 56:4-12.)

intent. Clauss testified that she expected figure 43 to be canceled in the '516 application at some point. However, it was standard practice at Foley Hoag to "prepare[] the figures once the case [was] indicated as allowable" to save money. (Clauss Dep. Tr., 64:14-18, 67:1-10.) This was the approach taken with the '266 and the '397 patents. The '516 application was transferred to Ropes & Gray before the claims were allowed, therefore Clauss was no longer involved at the time she would normally have been expecting the figure to be corrected. Lilly asserts, however, that Clauss had a duty to inform the PTO of the error earlier than allowance because she "made arguments for patentability based on the disclosure of IκB and/or IκB-encoding DNA." (Docket # 402 ¶ CF291.) It points to two separate responses to PTO Office Actions to support this claim.

(1) Clauss' Testimony on Materiality

First, Lilly cites a response filed June 10, 1998, in which Vincent stated that the application provided "ample evidence . . . to fully enable those skilled in the art to practice the invention with respect to activation of expression of IκB." (Docket # 397 ¶ FF97.) Clauss admitted that, when this response was filed, the then existing claims called for an agent affecting NF-κB activity that consisted of all or a portion of DNA encoding IκB or all or a portion of IκB. (Clauss Dep. Tr., 72:16-73:12.) Clauss testified that she "[p]robably" considered figure 43 material to those claims. (Id. at 72:16-73:12.)

However, this response was signed by Vincent, not Clauss.[45] In addition, the

[45] Dr. Clauss' signature appears only on the response attesting to the "Certification of Facsimile." (DTX 2 at ADL517.)

response not only canceled the claims calling for an agent based on the sequence information of figure 43, but the remainder of the paragraph cited by Lilly discussed the binding of the NF-κB-IκB-α complex in general and not the use of an agent based on the sequence of IκB-α. (DTX 2 at ADL529; compare id. at ADL465, claims 90, 92, with id. at ADL519 (canceling same).) Therefore, Clauss' admission that figure 43 was material to claims 90 and 92 does not establish an intent to mislead. These two claims, forwarded from the previous patent attorneys and which made the error in figure 43 material, were being canceled in the response filed by Foley Hoag.

(2) Clauss' Response to Office Action

A little over a year later, on September 17, 1999, Clauss responded to a final PTO Office Action and defended the sufficiency of the disclosure with regard to gene therapy, explaining that an "expression vector containing IκB-encoding DNA can be introduced into an individual" and that "IκB itself . . . can also be introduced into cells to inhibit NF-κB . . . ." (DTX 2 at ADL702.) Lilly correctly points out that the only disclosure in the specification of such "IκB encoding DNA" is purportedly found in figure 43. In addition, it asserts that Clauss was aware that the figure was not IκB-α when she defended the specification, and she was also aware that Ariad would lose the benefit of the longer patent term if they had to re-file the application.

Like Hausdorff's silence at PTO interviews, Clauss' failure to inform the PTO in September 1999 of the error in figure 43 is troubling. However, this is a single error in a long and complicated patent prosecution. It is easy in hindsight to portray a failure to act as something more than a mistake, oversight or negligence. Molins, 48 F.3d at

1181 (expressing concern about "the ease with which a relatively routine act of patent prosecution can be portrayed as intended to mislead or deceive."). I do not find that Lilly has met its burden to show by clear and convincing evidence that Clauss made a deliberate decision to withhold the information from the PTO. Compare M. Eagles, 439 F.3d at 1341 ("[A] failure to disclose a prior art device to the PTO, where the only evidence of intent is a lack of a good faith explanation for the nondisclosure, cannot constitute clear and convincing evidence sufficient to support a determination of culpable intent."), with Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Inc., 394 F.3d 1348, 1354 (Fed. Cir. 2005) (finding intent where applicant withheld relevant prior art for the PTO while at the same time disclosing it to the Food and Drug Administration in seeking approvals to sell device covered by patent).

Even though the error in figure 43 was material, Lilly has failed to meet the threshold showing necessary to prove intent and thus has failed to prove inequitable conduct.

6. Evidence of Inventor Baldwin's Intent to Conceal References

The elements of inequitable conduct predicated on a failure to disclose material prior art are identical to those discussed supra, p. 21, Lilly must show by clear and convincing proof both (1) knowledge by the applicant of the prior art and its materiality; and (2) an intent to mislead the PTO. Molins, 48 F.3d at 1178; M. Eagles, 439 F.3d at 1341. Lilly identifies only Dr. Baldwin as possessing both the knowledge and intent necessary to meet the threshold for inequitable conduct. (See Docket # 397 ¶¶ FF139-49.) In particular, it argues that Baldwin was aware of his duty to disclose yet

intentionally failed to disclose the information on known NF-κB inhibitors based on his deposition testimony:

> Q. Did you at any time consider disclosing your findings regarding Resveratrol in those experiments to the United States Patent Office?
>
> A. I mean I -- I considered it, but I -- again, I feel like that one would inundate the patent office with every report of -- of things that affect NF-κB one way or the other. It's -- you can do a search on NF-κB and it's endless.
>
> Q. Why is it you considered disclosing your findings regarding the effect of Resveratrol in your experiments to the United States Patent Office?
>
> A. Well, we signed -- we signed this document that says that was our obligation to do so at some point.

(Baldwin Dep. Tr. 171:16-172:5.) This is a slender thread on which to hang a claim of inequitable conduct. Ultimately, it fails because Lilly has not established that Baldwin was aware of the materiality of the withheld information.

There is no question that Baldwin was aware of the prior art, he was a co-author of the papers describing it. No evidence, however, suggests that Baldwin was aware of the materiality of the information in the legal sense. Baldwin is a scientist, not a patent attorney. His testimony admits to knowledge of his general duty to disclose "findings regarding [his] experiments," but Lilly fails to show that he had any understanding that a few short references to prior art compounds in a review paper had relevance to inherent anticipation or that he was aware that they had not already been disclosed. In order to show the necessary intent, Lilly would first have to show that Baldwin not only understood the need to disclose, but understood not only the concept of inherent

anticipation, but also that there was no need for contemporaneous recognition. Without such a showing, there is no reason to believe that Baldwin would understand, for example, that his statement that glucocorticoids had been used "for decades" could be relevant to the patent on his co-discovery of the mechanism by which NF-κB and IκB-α interact to suppress the expression of certain genes. A plain reading of Baldwin's testimony only admits to an understanding of the need to disclose the results of his current experiments, not his knowledge of the historical use of the same compounds.

Since the evidence fails to establish either knowledge of materiality or a motive to conceal, Baldwin's decision not to disclose background information concerning his current research is insufficient to prove by clear and convincing evidence an intent to deceive the PTO, and thus inequitable conduct.

C. Lilly's Prosecution Laches Defense

Lilly asserts that the sixteen-year delay between the initial filing of the application that eventually became the '516 patent and its issuance is unreasonable and unexplained, and resulted in material prejudice to the public and to litigants. It therefore argues that the '516 patent is unenforceable under the equitable defense of prosecution laches. This defense is based on the theory that a patent applicant should not be allowed to abuse the procedures for obtaining a patent in a way that unreasonably extends the patent grant and delays the release of the patented technology into the public domain.[46]

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[46] Prior to June 1995, patent owners who experienced a long examination period before the patent issued in effect obtained an extension of the term of their patent grant. This occurred because the term of the patent grant was seventeen years from

1. The Legal Standard for a Finding of Prosecution Laches

Obtaining a patent is often a lengthy process, with an average pendency in 2006 between application and either abandonment or grant of a U.S. Patent of over thirty-one months.[47] An inventor can deliberately extend the examination period while preserving the original priority date through a number of techniques, including responding to PTO actions as slowly as possible, filing continuation applications, and/or abandoning and refiling applications.

Federal courts have long recognized that excessive delay by an inventor in the prosecution of a patent may render it unenforceable. See Woodbridge v. United States, 263 U.S. 50, 63 (1923); Webster Elec. Co. v. Splitdorf Elec. Co., 264 U.S. 463, 466 (1924). However, a series of recent Federal Circuit decisions make clear that the

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the date of issuance; however a patent owner is granted priority on his or her invention from at least the date of application. Thus, a patent owner who experienced a long examination period could potentially reap the rewards of a larger pool of infringing defendants or a larger market from which to collect royalties.

In 1994 Congress changed the patent term from seventeen years from date of issuance to twenty years from date of application. This greatly reduced the ability of patent holders to create so-called "submarine" patents, that is, patented technology that remains unpublished until it surfaces years after application and surprises the market and effectively eliminates the issue of prosecution laches for patent applications filed after June 7, 1995. See Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809, codified at 35 U.S.C. § 154(a)(2). In addition, prior to 1999 patent applications were kept confidential by the PTO, with the result that potential infringers had no notice of a pending patent during its pendency. The 1999 American Inventors Protection Act provided for the publication of many patent applications 18 months after filing, giving potential infringers notice of pending patents in some cases. See Pub. L. No. 106-113, 113 Stat. 1501, codified at 35 U.S.C. § 122(b).

[47] See U.S. Patent and Trademark Office, Performance and Accountability Report (Fiscal Year 2006) at 22, available at http://www.uspto.gov/web/offices/com/annual/ (last visited July 2, 2007).

defense of prosecution laches will only succeed in extraordinary circumstances. See Symbol Techs. Inc. v. Lemelson Med., 277 F.3d 1361 (Fed. Cir. 2002) ("Symbol I"); Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found., L.P., 301 F. Supp. 2d 1147 (D. Nev. 2004) ("Symbol II"); Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found., LP, 422 F.3d 1378, 1385 (Fed. Cir. 2005) ("Symbol III") (collectively the "Symbol Cases"). It is not enough for a defendant to show sequential divisional applications on various aspects of the invention, nor is it enough to merely show refiling of rejected claims or the use of continuation applications to add new subject matter. See Symbol III, 422 F.3d at 1385. On the other hand, extreme delay extending the application process from 18 to 39 years, filing an application after allowance to postpone issuance, or repetitive filings that show a pattern of unjustifiably drawn out prosecution may constitute abuse of the patent system such as to amount to prosecution laches. Id. at 1386.

2. Analysis of Delays in the Prosecution of the '516 Patent

Lilly alleges that Ariad and/or their attorneys took advantage of PTO procedural rules to delay prosecution of the '516 patent in a manner that requires equitable relief from this court. Because there is no evidence that Ariad violated any specific rule or that it intentionally delayed prosecution of the '516 patent, Lilly asks this court to examine the "totality of the circumstances" to conclude that there was unreasonable and unexplained delay sufficient to trigger laches. Symbol III, 422 F.3d at 1385. In particular, Lilly points to: (1) Ariad's refiling of continuation applications rather than appealing the PTO's final rejection of claims; (2) extending the time to respond to office

actions to the maximum six-month period allowed by statute; (3) prosecuting the claims to the invention in multiple applications and abandoning those attempts when the claims were rejected by the PTO; and (4) Ariad's use of transitional rules to avoid a shortened patent term.

a. Requirement to File an Appeal

Lilly has cited no authority to support its assertion that an applicant's decision to abandon an application and file a continuation application, rather than appeal the examiner's rejection of its claims, is an indication of unreasonable and unexplained delay in prosecution. Indeed, the continued examination of applications is expressly provided for by statute[48] and described as an alternative to appeal by the PTO. MPEP § 706.07(h) (8th ed., rev. 5, Aug. 2006) ("If an applicant files a request for continued examination under this section after appeal, . . . it will be treated as a request to withdraw the appeal and to reopen prosecution of the application"). Lilly asserts that an appeal would have expedited prosecution and that "[t]here must be an obligation to take a timely appeal." (Def.'s Pre-Trial Br. (Docket # 362) at 19.) In the absence of evidence or case law to support these contentions, I decline to find that a decision not to appeal a final rejection constitutes an unreasonable or unexplained delay in prosecution.[49]

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[48] See 35 U.S.C. § 132 ("Notice of rejection; reexamination.").

[49] The accuracy of Lilly's assertion that an appeal would have expedited prosecution is dubious. The Practising Law Institute advises practitioners receiving a final rejection to file a continuation application because, "[t]he backlog at the Board of Patent Appeals is often several years. . . . If, after the occurrence of one or more in-person interviews with an examiner (and supervising examiner if possible), as well

b. Six Month Response to Office Actions

Lilly next claims that Ariad's use of the full six-month period provided by statute (35 U.S.C. § 133; see also MPEP § 710.02(a)(1)) to respond to Office Actions, rather than responding in the shortened regulatory period of three-months set by the PTO (MPEP § 710.02(b)), should be considered evidence of unreasonable delay. Again, Lilly fails to cite any support for this proposition, nor does it show that use of the full six-month period is unusual or atypical in patent prosecution generally. Rather, Lilly proposes that the additional time taken by Ariad in responding to the PTO compounds the other unreasonable delays they allege in prosecuting the patent. Because I do not find the total time to prosecute the '516 patent unreasonable (see infra), the use of the full statutory period to respond to Office Actions is not unreasonable.

c. The Pre-'898 Applications

Finally, Lilly points to the number of abandoned and refiled applications concerning the subject matter of the '516 patent as evidence of unreasonable and unexplained delay. Specifically, Lilly points to the sixteen-year delay and the eight abandoned applications between the first Ariad application and the issuance of the '516 patent. Between January 1986 and April 21, 1989, the date found by the jury to be the effective filing date of the '516 patent, Ariad filed seven patent applications. These seven applications were eventually abandoned after being consolidated into the

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as the filing of one or more continuation applications, it is clear that an important application will never get allowed by the examiner, it may be worth filing the appeal if the applicant is willing to wait for years." Jeffrey R. Kuester, Prosecuting a Patent That Holds up in Litigation (or, Destroying a Patent Unaware), 669 PLI/Pat 1033, 1070 (West 2001).

07/791,898 application, filed November 31, 1991. Ariad describes the filing of these continuation-in-part applications as reasonable in order to "add further material regarding the inventors' ongoing work with NF-κB, which had rapidly advanced the field." (Pls.' Supl. Trial Brief (Docket # 360) at 20 n.14.) The Federal Circuit specifically noted that such filings are common and justified as the development of an invention progresses. Symbol III, 422 F.3d at 1385. Therefore, I do not find the applications prior to the '898 application to be unreasonable or unexplained under these circumstances.

d. Post Development Applications

Thirteen months after the '898 application was filed, the examiner issued a restriction requirement, finding the original claims were directed toward multiple inventions. (See DTX33 at ADL15159-70, ADL15166.) Ariad elected to pursue a subset of its claims that addressed a method of inducing gene expression. (Id.) The examiner ultimately rejected all pending claims in a final Office Action dated July 6, 1994. (Id. at ADL15222-30.) Rather than appealing this decision, Ariad chose to file a continuation application, 08/418,266, on April 6, 1995. The inventions contained within this application eventually resulted in three U.S. patents: (1) 5,804,375, issued September 8, 1998 claiming methods of identifying an antagonist of gene transcription; (2) 6,150,090, issued November 21, 2000, claiming an improved assay for protein-DNA binding; and (3) the '516 patent, issued June 25, 2002. (DTX 3300.)

(1) Prejudice to Public Rights

While prejudice to intervening public and private rights is a factor in determining laches, Ariad diligently, albeit serially, pursued the '898 application to obtain three patents on the inventions disclosed. Nothing in the statute or regulations requires that an applicant pursue all of his or her inventions in parallel. Indeed, the granting of the first patent might well be necessary for an inventor with limited resources to fund the prosecution of the remaining claims. Here, the time between each of the three patents granted was only two years, and specification was public for only four years while the scope of the claims was uncertain. This is a far cry from the almost 30-year period of uncertainly between the disclosures first made public by Lemelson in his 1962 and 1963 patents and the claims finally granted in 1989 and the early 1990s on those same disclosures. See Symbol II, 301 F. Supp. 2d at 1155-56. In addition, there is no evidence that Ariad specifically tailored its claims to cover intervening inventions by Lilly or others as the court found Lemelson had done with his late 1980s and 1990s claims. Id. at 1156. Given Ariad's diligent pursuit of the three patents eventually granted, I do not find the four-year period, during which the scope of what was to be claimed and what was to be dedicated to the public was uncertain, unreasonable or unexplained.

e. Use of Transitional Rules

Lilly also suggests that Ariad's use of a provision in the 1995 transitional rules that allowed it to maintain a seventeen-year patent term from date of grant and their petitioning the examiner to withdraw his final rejection of their application to avoid loss

of potential patent term should be considered in the determination of prosecution laches. However, Ariad's desire to obtain the maximum term for its patent grant, particularly when the rules were being changed, is neither unreasonable nor unexplained. Indeed, Congress recognized the potential unfairness of changing the rules mid-stream and provided for transitional rules available to all inventors in similar circumstances.[50] Therefore, I do not find Ariad's actions to maximize the term of their patent grant under the transitional rules relevant to determining laches.

Nothing in the prosecution history of the '516 patent shows the kind of willful conduct and deliberate delay by Lemelson found by the court to require equitable relief in Symbol II.[51] While the prosecution of the '516 patent involved multiple applications, numerous interactions with the PTO and the significant passage of time, the inventors

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[50] Title 35 U.S.C. § 154(c)(1) (2002) ("The term of a patent that is in force on or that results from an application filed before the date that is 6 months after the date of the enactment of the Uruguay Round Agreements Act shall be the greater of the 20-year term as provided in subsection (a), or 17 years from grant.").

[51] It appears that Lemelson's conduct in the Symbol Cases represents the only time a district court found a prosecution delay unreasonable and unexplained enough to trigger prosecution laches. See Kothmann Enters., Inc. v. Trinity Indus., Inc., 2006 WL 89838, at *31 (S.D. Tex. Jan. 13, 2006) (comparing Symbol II to six cases with prosecution delays ranging between seven and fifteen years, but where laches was not found). While Lilly traces the prosecution history of the '516 patent in excruciating detail, it fails to provide any evidence showing that this history was atypical of patents in its field or of similar scope. The thirteen years between the '486 application, found by the jury to be the effective date of the '516 patent and its issuance, is significantly less than the 18- to 39-year delay in the Symbol Cases. In addition, there is no evidence that Ariad refiled applications after its claims were allowed; rather, it pursued its inventions in the face of multiple rejections of most of its claims. Cf. Symbol III, 422 F.3d at 1385 ("[R]efiling an application solely containing previously-allowed claims for the business purpose of delaying their issuance can be considered an abuse of the patent system.").

were seeking broad patent protection on evolving discoveries involving many inventions. Lilly has failed to show that this conduct was unreasonable or unexplained under the circumstances. This court does not find prosecution laches that would bar enforcement of the '516 patent.

IV. Conclusion

Because the four claims found infringed by the jury do not encompass unpatentable subject matter and the patent is not invalid due to inequitable conduct or prosecution laches, the '516 patent is valid and enforceable.

Judgment may be entered for plaintiffs in accordance with the verdict of the jury and the court's findings of fact and conclusions of law.

____July 6, 2007____
DATE

/s/Rya W. Zobel
RYA W. ZOBEL
UNITED STATES DISTRICT JUDGE