United States District Court,
N.D. California.

CARNEGIE MELLON UNIVERSITY and & Three Rivers Biologicals,
Inc. Plaintiffs.
v.
HOFFMANN-LA ROCHE INC., Roche Molecular Systems, Inc., Roche Diagnostic Systems, Inc., Roche Biomedical Laboratories, Inc., Laboratory Corporation of America Holdings, the Perkin-Elmer Corporation, Chiron Corporation,
and Cetus Oncology Corporation Defendants.

No. C-95-3524 SI

March 31, 1997.

ORDER GRANTING AND DENYING IN PART ROCHE AND CHIRON DEFENDANTS' REQUESTED CLAIM CONSTRUCTION AND GRANTING AND DENYING IN PART PLAINTIFFS' REQUESTED CLAIM CONSTRUCTION

ILLSTON**, J.**

The Court heard argument on the Roche defendants' motion for claim construction, Chiron defendants' motion for claim construction, and plaintiffs' motion for claim construction. Having considered the arguments of counsel and the papers submitted, the Court hereby grants and denies in part the Roche defendants' and Chiron defendants' requested claim construction, and grants and denies in part the plaintiffs' requested claim construction.

BACKGROUND

Plaintiffs Carnegie Mellon University and Three Rivers Biologicals, Inc. allege that the defendants have infringed claims 1-6, 10-19 and 22-40 of U.S. Patent No. 4,767,708 (the '708 Patent, entitled "Enzyme Amplification and Purification") and claims 1-2, 11-12, 14-15, 17-18, and 32-34 of U.S. Patent No. 5,126,270 (the '270 Patent, entitled "Enzyme Amplification and Purification"). The patents-in-suit relate to recombinant plasmids for the expression of an enzyme identified in the '708 patent as "DNA polymerase I," processes related to the construction of such plasmids, and processes related to the culturing of host cells containing such plasmids. FN1 Both patents derive from the same original application. The '708 Patent issued from a "parent" application filed on August 7, 1984, and the '270 Patent issued from a "continuation" application that was filed on November 5, 1987.

FN1. The '708 Patent does not disclose the sequence of a DNA polymerase I molecule or claim the DNA polymerase I enzyme itself. *See* Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1206 (Fed.Cir.) ("Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics

sufficiently distinguish it."), *cert. denied,* Genetics Inst., Inc. v. Amgen, Inc., 502 U.S. 856 (1991); Fiers v. Revel, 984 F.2d 1164, 1168-69 (Fed.Cir.1993).

Plaintiff Carnegie Mellon University is the record owner of the patents-in-suit, and plaintiff Three Rivers Biological, Inc. alleges that it was for a period of time an exclusive licensee of the patents-in-suit.FN2 The plaintiffs seek damages for infringement and inducement of infringement of the patents-in-suit and a permanent injunction against infringement and inducement of infringement by the defendants.

FN2. The '708 Patent originally issued naming Edwin G. Minkley, Jr. and William E. Brown as joint inventors. A Certificate of Correction subsequently named Dr. Minkley as the sole inventor.

I. Technological Background FN3

FN3. The Court's overview of DNA technology is excerpted from the Federal Circuit's decision in In re O'Farrell, 853 F.2d 894, 895-97 (Fed.Cir.1988).

Proteins are biological molecules of enormous importance. Proteins include enzymes that catalyze biochemical reactions; major structural materials of the animal body; and many hormones. Numerous patents and applications for patents in the field of biotechnology involve specific proteins or methods for making and using proteins. Many valuable proteins occur in nature only in minute quantities, or are difficult to purify from natural sources. Therefore, a goal of many biotechnology projects is to devise methods to synthesize useful quantities of specific proteins by controlling the mechanism by which living cells make proteins.

Protein molecules are composed of long chains of amino acids. To make a protein molecule, a cell needs information about the sequence in which the amino acids must be assembled, since the sequence of amino acids determines the characteristics of the protein.

The cell uses a long molecule, DNA, to store this information. DNA molecules do not participate directly in the synthesis of proteins. Instead, DNA acts as a permanent "blueprint" of all of the genetic information in the cell, and exists mainly in extremely long strands (called chromosomes) containing information coding for the sequences of many different proteins, most of which are not being synthesized at any particular moment. DNA strands are made up of nucleotides, the sequence and combination of which in the DNA strand specifies the particular sequence of amino acids in a particular protein. The specific region of DNA on the chromosome that codes for the sequence of a particular protein is called a gene.

In order to make a specific protein by expressing its cloned gene in bacteria,FN4 several technical hurdles must be overcome. First the gene, or DNA coding region, for the specific protein must be isolated for cloning. Next the isolated gene must be introduced into the host bacterium. This can be done by incorporating the gene into a cloning vector. A cloning vector is a piece of DNA which can be introduced into bacteria and which will then replicate itself as the bacterial cells grow and divide. One type of cloning vector is a plasmid, a small circular loop of DNA found in bacteria, separate from the chromosome, that replicates like a chromosome. Because of its small size, a plasmid is convenient for the molecular biologist to isolate and work with.

FN4. "The process of making large quantities of identical copies of a gene (or other fragment of DNA) by introducing it into [bacteria] and then growing those cells is called *cloning* the gene. After growing sufficient quantities of the transformed bacteria, the biotechnologist must induce the transformed bacteria to *express* the cloned gene and make useful quantities of the protein." *In re O'Farrell,* at 898 (emphasis in original).

Recombinant DNA technology is used to modify plasmids by splicing in (recombining) cloned genes and other useful segments of DNA containing control sequences. Short pieces of DNA can even be designed to have desired nucleotide sequences, synthesized chemically, and spliced into plasmids. A plasmid constructed by the molecular geneticist can be inserted into bacteria, where it replicates as the bacteria grow.

II. Motions for Claim Construction

Defendants Hoffmann La-Roche Inc., Roche Molecular Systems, Inc., Roche Diagnostic Systems, Inc., Roche Biomedical Laboratories, Inc., Laboratory Corporation of America Holdings, and The Perkin-Elmer Corporation (the Roche defendants) and defendants Chiron Corporation and Cetus Oncology Corporation (the Chiron defendants) filed separate motions for claim construction, requesting the Court to interpret the claims of the '708 and '270 patents as follows:

(1) The term "DNA polymerase I" as used in the claims of the '708 Patent means an enzyme that:

(a) is lethal or debilitating to growth of the host cell strain when expressed from a multicopy plasmid, and

(b) possesses three enzyme activities, namely

(i) polymerase activity,

(ii) 5'-3' exonuclease activity, and

(iii) 3'-5' exonuclease activity.

(2) The term "plasmid" as used in the claims of the '708 Patent means "a multicopy plasmid containing the entire nonmutated structural gene coding region for the expression of the complete DNA polymerase I enzyme."

(3) The process for constructing a plasmid in claim 25 of the '708 Patent requires that the complete structural gene coding region for expression of DNA polymerase I be excised from its bacterial source in one piece and inserted into the vector plasmid in one piece.

(4) The term "plasmid" as used in the claims of the '270 Patent means "a multicopy plasmid containing the entire nonmutated structural gene coding region for the expression of the complete DNA polymerase I enzyme, which is lethal or debilitating to the growth of the host cell strain when expressed from a multicopy plasmid and has the following three activities: polymerase activity, 5'-3' exonuclease activity, and 3'-5' exonuclease activity."

Plaintiffs also filed their own motion for claim construction, requesting the Court to adopt their proposed interpretation of the patent claims as follows:

(1) The term "DNA polymerase I" as used in the claims of the '708 Patent means a DNA polymerase enzyme having nick-translation activity (i.e., 5'-3' exonuclease activity and DNA polymerizing activity). The term "DNA polymerase I" does not require that the enzyme (a) be lethal, debilitating, or inhibiting to the growth of the host cell strain when expressed from a multicopy plasmid, or (b) have 3'-5' exonuclease activity.

(2) The phrase "complete structural gene coding region" as used in claims 1 and 25 (and asserted dependent claims thereto) of the '708 Patent requires that the recombinant plasmid have the complete structural gene coding region for the expression of DNA polymerase I. The phrase "complete structural gene coding region" does not require that the structural gene coding region of the recombinant plasmid be "entire" (i.e., have no missing nucleotide bases) or "non-mutated" (i.e., without a single mutation).

(3) The steps of "excising enzymatically from the DNA molecule the complete structural gene coding region" and "cloning said complete structural gene coding region into a vector plasmid" in claim 25 of the '708 Patent requires only that those two steps be done and does not limit the way in which these steps are to be performed. Claim 25 does not require that the gene coding region be excised from the bacterial source in one piece or inserted into the vector plasmid in one piece.

(4) The phrase "recombinant plasmid providing for nick-translation activity" in claims 1, 11, and 14 of the '270 Patent and the phrase "recombinant plasmid containing a DNA coding sequence for expression of nick-translation activity" in claim 17 of the '270 Patent require that the multicopy plasmids contain a gene coding region for expression of nick-translation activity. The phrase "recombinant plasmid containing a DNA coding sequence for the expression of DNA polymerase activity" in claims 32 and 34 of the '270 Patent requires that the multicopy plasmid contain a gene coding region for the expression of DNA polymerizing activity. There is no basis for reading into these claims the requirements that the recombinant plasmids contain a complete structural gene coding region without deletions or mutations, that the DNA polymerase expressed from the plasmid be DNA polymerase I, or that the DNA polymerase I have 3'-5' exonuclease activity and be lethal, debilitating or inhibiting to growth of host cells.

On January 14, 1997, the Court conducted a hearing on the parties' motions for claim construction pursuant to Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed.Cir.1995) (en banc), *aff'd,* 116 S.Ct. 1384 (1996).

LEGAL STANDARD

Proper construction of patent claims is to be made by the trial court as a matter of law. Markman, 52 F.3d at 979. In determining the proper construction of a claim, the Court has numerous sources, intrinsic and extrinsic, that it may properly utilize for guidance.

The Court begins with the intrinsic evidence of record, consisting of the patent itself, the patent specification, and, if in evidence, the prosecution history. Unique Concepts, Inc. v. Brown, 939 F.2d 1558, 1561 (Fed.Cir.1991). The Court must examine the words of the claims themselves, both asserted and unasserted, to define the scope of the patented invention. *See* Bell Communications Research, Inc. v. Vitalink Communications Corp ., 55 F.3d 615, 620 (Fed.Cir.1995). Although words in a claim are generally

given their ordinary and customary meanings, a patentee is free to act as its own lexicographer provided that the patentee's special definition is clearly stated in the patent specification or prosecution history. Hormone Research Found., Inc. v. Genentech, Inc., 904 F.2d 1558, 1563 (Fed.Cir.1990), *cert. dismissed,* 499 U.S. 955 (1991).

To determine whether the patentee has used any claim terms in a manner inconsistent with their ordinary meanings, the Court must in each case review the patent specification. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996). The specification is highly relevant and typically dispositive of the claim construction analysis. *Id.*

Finally, the Court may consider the prosecution history of the patent, if in evidence. The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution. *Southwall Technologies, Inc. v. Cardinal IG Co.,* 54 F,3d 1570, 1576 (Fed.Cir,), *cert. denied,* 116 S.Ct. 515 (1995).

In most situations, an analysis of the intrinsic evidence alone will resolve claim construction disputes. Vitronics, 90 F.3d at 1583. Reliance on extrinsic evidence is unnecessary and improper when the disputed terms can be understood from a careful reading of the public record. Id. at 1584. Nor may such evidence be used to vary the claim terms from how they are defined, even implicitly, in the specification or prosecution history. Id. at 1584-85.

DISCUSSION

I. The Term "DNA Polymerase I" in the '708 Patent

A. *Lethal or Debilitating to Growth of the Host Cell Strain*

The defendants assert that "DNA polymerase I," as the term is used in the '708 Patent, is limited to an enzyme that is lethal or debilitating to growth of the host cell strain when expressed from a multicopy plasmid. The plaintiffs assert that the defendants' interpretation is at odds with the express language of the claim, which contains no reference to an enzyme that is "lethal" or "debilitating." The plaintiffs urge that the term "DNA polymerase I" must be interpreted as written in the claim, without considering the discussion of lethality in the specification or prosecution history.

The plaintiffs are correct that the Court must begin with an analysis of the claim language. Claim 1 of the '708 Patent claims:

A recombinant plasmid containing a cloned complete structural gene coding region isolated from a bacterial source for the expression of DNA polymerase I, under operable control of a conditionally controllable foreign promoter functionally linked to said structural gene coding region, said foreign promoter being functional to express said DNA polymerase I in a suitable bacterial or yeast host system.

'708 Patent at col. 9, line 65 to col. 2, line 4. Neither claim 1 nor any of the other claims in the '708 Patent makes reference to DNA polymerase I that is "lethal or debilitating to the growth of the host cell strain when expressed from a multicopy plasmid." Nevertheless, the Court must also consider the specification to determine how the patentees used the term "DNA polymerase I." Vitronics, 90 F.3d at 1582 ("it is *always*

necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning.") (emphasis added). The Court therefore turns to the specification for guidance in construing the term "DNA polymerase I."

As indicated by the defendants, the specification contains numerous references to DNA polymerase I's toxic effects on cell growth when produced at levels above the natural amount. In particular, the patentees observed that "[t]he prior art ha[d] failed to clone polA, the structural gene which codes for DNA polymerase I (Pol I), onto a multicopy plasmid because the resultant increase above the natural level of expression of Pol I was known to be lethal to a host bacterium...." '708 Patent at col. 1, lines 14-18. The patentees continued:

This invention will be of utility specifically in those instances, such as with polA, where expression from the natural promoter of the gene of interest is not tightly regulated and where cloning of the intact structural gene onto a high copy number plasmid is impossible because of a lethal or debilitating overproduction of the corresponding gene product.

Id. at col. 4, lines 6-13. *See also* id. at col. 3, lines 24-26 ("After a limited period of such expression, the cells die or become debilitated or growth inhibited.").

The plaintiffs contend that the patentees' discussion of lethality in the specification is an extraneous limitation that cannot be read into the patent claims. *See* E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co., 849 F.2d 1430, 1433 (Fed.Cir.), *cert. denied,* 488 U.S. 986 (1988). The plaintiffs emphasize that the question before the Court is not one of claim validity, i.e., whether the claim would be patentable over the prior art if the suggested restriction were not applicable; instead, the question before the Court is the meaning of claim terms. *See* Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418, 1422-23 (Fed.Cir.), *cert. denied,* 115 S.Ct. 500 (1994).

However, contrary to the plaintiffs' assertions, incorporation of the lethality characteristic in the claims of the '708 patent does not import an extraneous limitation from the specification into the '708 Patent claims, but rather defines a term expressly contained in the '708 Patent claims (i.e., "DNA polymerase I"). *See* Du Pont, 849 F.2d at 1433 ("By 'extraneous,' we mean a limitation read into a claim from the specification wholly apart from any need to interpret what the patentee meant by *particular words or phrases in the claim*.") (emphasis added). The Court therefore construes the term "DNA polymerase I" consistently with the way the patentees used the term in the specification and prosecution history.

The specification makes clear that "DNA polymerase I" was understood at the time of the patent application to be an enzyme that is lethal or debilitating to the growth of the host cell strain when expressed from a multicopy plasmid. The patentees did not describe lethality as an extraneous limitation. Instead, the patentees understood lethality to be a defining characteristic of DNA polymerase I. *See* '708 Patent at col. 2, lines 43-46 ("This is a significant discovery of the present invention, since it eliminates or greatly reduces the unregulated expression of Pol I, *which would otherwise be lethal to the cell*.") (emphasis added). The Court must interpret DNA polymerase I as the term is defined in the specification to incorporate the lethal and debilitating effects of the enzyme on host cell strain growth. *See, e.g.,* Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251 (Fed.Cir.1989).

The prosecution history also supports the defendants' proposed construction of "DNA polymerase I." The patent applicants distinguished their invention from the prior art on the ground that the applicants' method

regulated the production of enzymes that were lethal or debilitating to bacterial cell growth:

The applicants agree that Joyce et al. (AR) teach the use of the lambda p_L promoter and the *lac* promoter for expression of a desired gene, both having activity which is conditionally controllable. However, applicants patentably distinguish over this teaching by utilizing the prior art method to produce a protein *which is lethal or debilitating to cell growth* when its gene is cloned onto a multicopy plasmid as is the case in the expression of DNA polymerase I.

'708 Prosecution History, Amendment dated December 2, 1986, at 13 (emphasis added). In addition, the applicants stated to the Examiner that "whatever the amount of DNA polymerase I which is produced, if it is lethal or debilitating it is within the scope of the invention and if it is not lethal or debilitating it is not within the scope of the invention." *Id*. at 4. The defendants argue that the term "DNA polymerase I" must be interpreted consistent with the patentees' representations to the Examiner. *See, e.g., Southwall,* 54 F.3d at 1576 ("The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution.").

The plaintiffs assert that the patentees' statements must be read in context. In particular, the statements quoted above were made to provide understanding of the claimed subject matter and satisfy the requirements of 35 U.S.C. s. 112.FN5 The plaintiffs contend that under Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211 (Fed.Cir.1995), the applicants' statement cannot be used to narrow the meaning of claim terms:

FN5. "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, to make and use the same...." 35 U.S.C. s. 112.

[W]hen claim changes or arguments are made in order to more particularly point out the applicant's invention, the purpose is to impart precision, not to overcome prior art. Such prosecution is not presumed to raise an estoppel, but is reviewed on its facts, with the guidance of precedent.
Id. at 1220.
Applying the principles set forth in *Southwall* and *Pall Corp*. to the facts of the instant case, the Court adopts the defendants' construction of the term "DNA polymerase I." FN6 Prior to the patentees' invention, scientists could not clone the structural gene coding region for DNA polymerase I (i.e., polA gene) onto a multicopy plasmid because of the enzyme's toxic effects on bacterial host cell growth. '708 Patent at col. 1, lines 14-20. To overcome the lethality problem, the patentees fused the cloned polA gene onto a foreign promoter subject to conditional control. Id. at col. 2, lines 35-40. The promoter functioned as a switch to decrease the production of DNA polymerase I so that the bacteria could grow and multiply. While the prior art had taught the use of promoters subject to conditional control for expression of a desired gene, the patentees used the prior art method to produce a protein which was lethal or debilitating to cell growth when cloned onto a multicopy plasmid (i.e., "DNA polymerase I"). '708 Prosecution History, Amendment dated December 2, 1986, at 13. *See also* '708 Patent at col. 2, lines 43-46. The prosecution history read alongside the specification thus supports the defendants' construction of the term "DNA polymerase I."

FN6. According to the Chiron defendants, the plaintiffs confuse two separate patent doctrines: claim construction and prosecution history estoppel. *See Southwall,* 54 F.3d at 1578 ("There is ... a clear distinction between following the statements in the prosecution history in defining a claim term[ ] and the

doctrine of prosecution history estoppel, which limits the expansion of the protection under the doctrine of equivalents when a claim has been distinguished over relevant prior art."). The Chiron defendants assert that *Southwall,* which discussed principles of claim construction, applies to the instant case instead of *Pall Corp.,* which discussed the doctrine of equivalents. The Court need not determine whether the Chiron defendants' reading of *Pall Corp.* and *Southwall* is correct. Assuming *Pall Corp.* to apply to the instant case, the Court finds that the prosecution history read as a whole supports the defendants' construction of the term "DNA polymerase I."

Ultimately, the plaintiffs provide no persuasive rationale for interpreting the disputed claim term in a manner inconsistent with the specification and prosecution history. The Patent and Trademark Office ("PTO") and the defendants relied on the patentees' representations, which the plaintiffs now seek to disclaim. The Federal Circuit has made clear that "claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers." *Southwall,* 54 F.3d at 1576. The Court therefore adopts the defendants' construction of "DNA polymerase I." FN7

FN7. The Court also rejects the plaintiffs' argument that the patentees' statement to the Examiner were erroneous statements by the patentees' attorney which cannot change the meaning of the patent claims as issued. In issuing the '708 Patent, the Examiner relied on the patentees' representation that "DNA polymerase I" is lethal or debilitating to growth of the host cell strain. The claim must therefore be construed consistent with the patentees' statements in the public record.

Alternatively, the plaintiffs emphasize the language of the patent claims as originally filed. The patentees submitted a number of claims to the PTO, some of which included references to DNA polymerase I's lethal and debilitating effects (e.g., claims 14, 34, 38, 39 and 40) and others of which did not (e.g., claims 1 and 25). The plaintiffs contend that under the rule of claim differentiation, the "narrow" claims citing the enzyme's lethal and debilitating effects must be interpreted distinctly from the "broad" claims containing no such references.

However, the plaintiffs provide no support for the contention that courts must differentiate between filed as opposed to issued claims. The doctrine of claim differentiation assumes that the PTO would not issue several claims of the same scope. The discrepancy in the claims *as filed* reflects the plaintiffs' drafting of the claims, not the PTO's independent judgment. Moreover, "[c]laim differentiation is a guide, not a rigid rule." Autogiro Co. v. United States, 384 F.2d 391, 404 (Cl.Ct.1967). In particular, "[i]f a claim will bear only one interpretation, similarity will have to be tolerated." *Id.* The patentees' definition of DNA polymerase I as lethal or debilitating to host cell strain growth is not limited in its application to a subset of the claims. To the contrary, the patentees' description of the enzyme is consistent throughout the patent specification and prosecution history. The only inconsistency that would arise is if the Court were to apply rigidly the doctrine of claim differentiation to the patentees' filed as opposed to issued claims. The Court declines to do so.

In addition, the plaintiffs assert that several of the claims that had contained references to lethality and growth inhibition were amended to eliminate such references. '708 Prosecution History, Amendment dated November 5, 1987, at 2, 6 (patentees deleted "containing a level of DNA polymerase which is lethal or inhibiting to the host strain" and "lethal or debilitating level of" from the filed claims); *id.,* Amendment dated December 28, 1987, at 2, 6. The plaintiffs contend that the amended claims must be construed as issued (i.e., without the references to lethality).

However, as the defendants indicate, the patentees amended the claims to overcome the Examiner's objection that the plaintiff had failed to teach the level at which DNA polymerase I becomes lethal. '708 Prosecution History, Office Action dated July 7, 1986, at 5 ("Applicants have failed to teach the concentration of polymerase I which results in cell lethality or inhibition."). The defendants correctly assert that there is a distinction between identifying a compound as lethal and specifying its lethal dose. By eliminating the claims' references to the *level* of lethality, the patentees overcame the Examiner's specific objection that the patentees had failed to teach the *level* of lethality; the patentees did not by amendment change the definition of DNA polymerase I clearly set forth in the specification as filed and as issued. *See, e.g., id.,* Specification as Originally Filed, at 4, lines 12-15 ("This is a significant discovery of the present invention since it eliminates or greatly reduces the unregulated expression of Pol I, which would otherwise be lethal to the cell."); '708 Patent at col. 2, lines 43-46 (same).

In sum, based on a review of the claim language, patent specification, and prosecution history, the Court construes the term "DNA polymerase I" as an enzyme that is lethal or debilitating to growth of the host cell strain when expressed from a multicopy plasmid.

B. *3'-5' Exonuclease Activity (The "Proofreading" Function)*

The parties agree that "DNA polymerase I," as defined in the patent, must perform at least two functions-polymerase activity and 5'-3' exonuclease (nick-translation) activity. The defendants assert that the term "DNA polymerase I" also encompasses a third function-3'-5' exonuclease activity (i.e., the "proofreading" function).

The invention is described as follows in the specification:

The present invention is directed to a novel plasmid containing the entire nonmutated structural gene coding region for the production of the complete pol I enzyme, *including both the Klenow fragment and the smaller fragment*.

'708 Patent at col. 2, lines 9-13 (emphasis added). The specification clarifies that:

[while] [t]he large or carboxylterminal fragment (the Klenow fragment) contains the polymerase and 3'-5' exonuclease functions ... the smaller fragment contains the 5'-3' exonuclease activity necessary for the nick-translation reaction of Pol I.

'708 Patent at col. 1, lines 56-60. The defendants assert that the definition of "DNA polymerase I" is express in the specification: "DNA polymerase I" is comprised of the Klenow fragment (i.e., the polymerase and proofreading functions) and the smaller fragment (i.e ., the 5'-3' exonuclease function necessary for nick-translation).

The plaintiffs characterize this discussion in the specification as "historic information" concerning the prior art, not a description of the present invention. The plaintiffs assert that this discussion described the prior work of Joyce and Grindley, who had cultivated DNA polymerase I using *E. coli* bacteria only. The plaintiffs emphasize that the patentees used the term "DNA polymerase I" in a manner not limited to *E. coli* and thus not "necessarily" the same as the prior usage. The Court disagrees. The specification clearly defines "DNA polymerase I" of the *present* invention to encompass both the Klenow and smaller fragments.

Id. at col. 2, lines 9-13. The specification furthermore makes reference to its earlier description of the Klenow and smaller fragments. *Id*. at col. 2, lines 13-14 ("*As stated above,* the smaller fragment is necessary for the nick-translation reaction of Pol I.") (emphasis added). The patentees clearly used the term "DNA polymerase I" in the specification to encompass the Klenow fragment, which contains polymerase and 3'-5' exonuclease functions, and the smaller fragment responsible for 5'-3' exonuclease activity.

The prosecution history also supports the defendants' construction of the term "DNA polymerase I." In the first office action, the Examiner rejected a number of the patentees' claims on the ground that the patentees provided enabling information for DNA polymerase I cultivated only in *E. Coli,* not other bacterial host strains. '708 Prosecution History, Office Action dated July 7, 1986, at 6. The patentees asserted in response that *B. subtilis,* a bacteria similar to *E. Coli,* was known to express enzymes that met the patentees' definition of DNA polymerase I. *Id.,* Amendment dated December 2, 1986, at 6. The patentees referred the Examiner to the following definition of "DNA polymerase I":

The Pol I molecule can be split into two enzymatically active fragments, a large fragment and a small fragment. The large or carboxylterminal fragment (the Klenow fragment) contains *the polymerase and 3'-5' exonuclease functions* whereas the smaller fragment contains the *5'-3' exonuclease activity* necessary for the nick-translation reaction of Pol I.

Id., Specification as Originally Filed at 2, lines 16-22 (emphasis added); *id.,* Amendment dated December 2, 1986, at 6. The specification makes clear that the term "DNA polymerase I" encompasses three functions: polymerase activity, 3'-5' exonuclease activity, and 5'-3' exonuclease activity.

The plaintiffs contend that the patentees' reference to the specification must be read in context:

Applicants have described a DNA polymerase I enzyme on page 2, lines 16-22, of the specification *as an enzyme consisting of a single polypeptide chain that is capable of 'nick translation' because it contains both 5' to 3' exonuclease activity and 5' to 3' DNA polymerizing activity*.

Id., Amendment dated December 2, 1986, at 6 (emphasis added). According to the plaintiffs, the patentees highlighted for the Examiner the essential features of "DNA polymerase I"-namely, 5'-3' exonuclease and polymerizing activity-expressly omitting 3'-5' exonuclease activity from their definition.

The plaintiffs' argument is unsupported by the subsequent correspondences between the Examiner and the patentees. In its second office action, the Examiner explicitly adopted the three-activity definition of DNA polymerase I contained in the original specification. *See id.,* Office Action dated May 5, 1987, at 6 ("However, it is considered that applicant's reliance upon Kornberg is misplaced because in Table 5.4, pol I of *B. subtilis* is not shown to contain 3 to 5 prime and 5 to 3-prime exonuclease activity and therefore does not meet *applicant's definition of pol I as stated at page 2, lines 16-22 in the specification* ....") (emphasis added). In a subsequent amendment to the patent application, the patentees failed to challenge the Examiner's description of "DNA polymerase I" as a three-activity enzyme, a characterization that the plaintiffs now allege to be erroneous. *Id.,* Amendment dated December 28, 1987, at 24. The Court therefore adopts the definition of "DNA polymerase I" contained in the original and final '708 Patent specifications and cited by the patentees and Examiner in their correspondences.FN8

FN8. The plaintiffs contend that the defendants' restrictive definition of "DNA polymerase I" would limit the '708 Patent to DNA polymerase from *E. coli* despite the Examiner's clear understanding that the claims

covered DNA polymerase I expressed from bacterial sources other than *E. coli*. *See* '708 Prosecution History, Office Action dated July 7, 1986, at 6 ("The claims as written read on the cloning, expression, isolation and purification of *all* DNA polymerase I enzymes and in *all* cloning host cell systems."). However, the record shows that "DNA polymerase I," as defined in the specification, is found not only in *E. coli,* but also in *M. luteus* and *S. pneumoniae*. '708 Prosecution History, Arthur Kornberg, *DNA Replication* 180 (1980); *id.,* Susana Martinez et al., *Cloning of a Gene Encoding a DNA Polymerase-Exonuclease of Streptococcus pneumonia* at 83-84 (1986).

II. The Phrase "Complete Structural Gene Coding Region" in Claims 1 and 25 of the '708 Patent

Claim 1 of the '708 Patent reads as follows:

A recombinant plasmid containing a cloned complete structural gene coding region ... for the expression of DNA polymerase I....

'708 Patent at col. 9, line 65 to col. 2, line 4. Claim 25 of the same patent also contains the phrase "complete structural gene coding region" in several places.

The parties dispute the proper construction of these phrases. The defendants assert that the "complete structural gene coding region" must be "entire" and "non-mutated," and that these phrases should be read to modify the word "plasmid" in Claim 1. The plaintiffs argue that the Court should focus on construing the phrase actually in Claim 1 ("complete structural gene coding region"), not on redefining the word "plasmid"; and that this phrase does not include the "entire" or "non-mutated" limitation.

Each of these points will be considered in turn.

A. "*Plasmid*" *vs.* "*Complete Structural Gene Coding Region*"

The defendants argue that the term "plasmid" as used in Claim 1 of the '708 Patent should be read to mean "a multicopy plasmid containing the entire nonmutated structural gene coding region for the expression of the complete DNA polymerase I enzyme." The plaintiffs contend that the Court should construe not the term "plasmid" but instead the phrase "complete structural gene coding region." The Court agrees with the plaintiffs that it must construe the phrase "complete structural gene coding region."

If the Court were to adopt the defendants' proposed construction, claim 1 of the patent would read as follows:

A recombinant *multicopy plasmid containing the entire nonmutated structural gene coding region for the expression of the complete DNA polymerase I enzyme* containing a cloned complete structural gene coding region ... for the expression of DNA polymerase I....

This would make for a redundant and contorted reading of the '708 Patent claims, which the Court does not adopt.

B. *The Meaning of* "*Complete Structural Gene Coding Region*"

The defendants assert that the DNA strand that serves as the blueprint for DNA polymerase I must be

"complete" (i.e., entire) and "nonmutated" (i.e., its nucleotide sequence has not been changed). Defs.' Joint Proposed Claim Construction, Tab A, at 1. Although the phrase which appears in Claims 1 and 25 does not itself include the words "entire" or "nonmutated," the defendants rely on the specification's description of the structural gene coding regionas "entire," "undamaged," and "nonmutated." *See, e .g.,* '708 Patent at col. 2, lines 9-13; id. at col. 2, lines 23-25. The defendants conclude that the '708 Patent encompasses only a plasmid containing a "complete" and "nonmutated" structural gene coding region.

In response, the plaintiffs assert that there is no basis for interpreting the term "structural gene coding region" as "entire" (i.e., no missing nucleotide bases) and "nonmutated" (i .e., no changes in the nucleotide sequence). The Court agrees. The '708 Patent claims expressly describe the structural gene coding region only as "complete," not as "entire" or "nonmutated"; the defendants infer these additional attributes from the description in the specification. Read in context, however, the specification supports the plaintiffs', not the defendants', proposed construction. In the specification, the patentees emphasized that the prior art had used a *mutated* form of the polA gene for expression of *the Klenow fragment* of DNA polymerase I:

Joyce and Grindley began their construction with a mutation of the polA gene located amino terminal to the Klenow fragment coding region. The polA gene was then further mutated by the removal of the portion of the gene upstream of the Klenow fragment so that the promoter was by necessity also removed with the gene fragment.... Thereby, a plasmid was produced capable of overproducing only the Klenow fragment of the Pol I molecule.

'708 Patent at col. 1, line 63, to col. 2, line 8. To distinguish their invention from the prior art, the patentees described their invention as a plasmid containing the entire *non-mutated* structural gene coding region for the production of the *complete DNA polymerase I enzyme*. Id. at col. 2, lines 9-13 ("The present invention is directed to a novel plasmid containing the *entire nonmutated* structural gene coding region for the production of the *complete Pol I enzyme,* including both the Klenow fragment and the smaller fragment.") (emphasis added). The specification thus makes clear that the patentees used the term "nonmutated" to refer to a change in the nucleotide sequence that expresses the complete DNA polymerase I, as opposed to only the Klenow fragment.FN9

FN9. The defendants emphasize that the plaintiffs' construction of the term "mutated" for purposes of the specification is at odds with their construction of the term "mutated" for purposes of claim 23 of the '708 Patent. *See* Pls.' Initial Claim Construction, Tab 1, at 28 (defining "mutated" as a change in the DNA nucleotide sequence). However, a patentee is free to act as its own lexicographer. Hormone, 904 F.2d at 1563. It is clear that the term "nonmutated" in the specification refers specifically to the absence of a change in the nucleotide sequence *that would preclude the expression of the complete DNA polymerase I enzyme*.

The prosecution history of the '270 Patent (i.e., the continuation patent) further supports the plaintiffs' construction of the term "gene coding region." The patentees amended the '708 Patent specification to omit the words "entire non-mutated" without objection from the Patent and Trademark Office. '270 Prosecution History, Amendment dated November 21, 1990, at 1. The PTO's failure to raise a "new matter" objection to the specification amendment is entitled to a weighty presumption of correctness. *See* Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1574-75 (Fed.Cir.1992). As such, the Court construes the phrase "complete structural gene coding region" from the '708 Patent claims as "complete structural gene coding region for the expression of DNA polymerase I," without the further requirements that the gene coding region be "entire" or "non-mutated."

III. The Process for Constructing a Recombinant Plasmid in Claim 25 of the '708 Patent

The parties dispute the specific process for constructing a plasmid set forth in claim 25 of the '708 Patent. Claim 25 reads as follows:

25. A process for constructing a recombinant plasmid for the expression of DNA polymerase I .... comprising the steps of:

excising enzymatically from a DNA molecule the complete structural gene coding region isolated from a bacterial source of said DNA polymerase I;

cloning said complete structural gene coding region into a vector plasmid....

'708 Patent at col. 10, line 60 to col. 11, line 6. The defendants assert that the complete structural gene coding region must be excised from its bacterial source *in one piece* and inserted into the vector plasmid *in one piece*.

The defendants cite the claim language, specification, and prosecution history in support of their construction of claim 25. The defendants emphasize the claim's description of the structural gene coding region as "complete." According to the defendants, the term "complete" in claim 25 suggests that the structural gene coding region must be removed and inserted in a single intact strand. *See also* '708 Patent at col. 2, lines 24-25 ("The novel plasmid of the present invention contains the entire and undamaged polA gene coding region enzymatically excised from a DNA molecule."). The defendants also rely on Figure 1 in the specification, which illustrates the removal of the gene coding region from the bacterial source through the use of restriction enzymes that cut at the ends of the gene coding region. *See* '708 Patent at Fig. 1; id. at col. 9, lines 21-24 ("The present invention can now be illustrated by the figures in which: FIG. 1 illustrates cloning of polA $^{+}$ onto a plasmid expression vector."). Finally, the defendants emphasize the patentees' statement to the Examiner that "the present invention relates to the cloning of an *intact* polymerase I gene onto a multicopy plasmid...." '708 Prosecution History, Amendment dated December 2, 1986 at 4 (emphasis added).

The Court rejects the defendants' efforts to limit claim 25 to a preferred embodiment of the invention. The Federal Circuit has held that "particular embodiments appearing in the specification will not generally be read into the claims." *Specialty Composites,* 845 F.2d at 987. The patentees claim the steps of "*excising enzymatically* from a DNA molecule the complete structural gene coding region" and "*cloning* said complete structural gene coding region into a vector plasmid." Claim 25 does not specify how the enzymes are to be excised or cloned. Figure I, which illustrates the placement of the enzymes at the ends of the gene coding region, merely describes a single embodiment of the invention.

The patentees' references to a "complete" structural gene coding region in claim 25 and an "intact" polymerase I gene in the prosecution history do not change the Court's position. Whether the gene coding region is excised and cloned in one piece or in multiple pieces, the polA gene is "complete" and "intact" if it is able to express the DNA polymerase I enzyme.FN10 The Court declines to read into claim 25 a requirement that the gene coding region be removed from its bacterial source or inserted into a vector plasmid in a single strand. Such a construction is not warranted by the patent, specification, or prosecution history.

FN10. In their joint proposed claim construction, the defendants define "complete" as follows: "A gene is 'complete' if it has the same number of nucleotides as the corresponding gene found in nature ." Defs.' Joint Proposed Claim Construction, Tab C, at 2.

IV. The Term "Plasmid" in the '270 Patent

The defendants request the Court to interpret the term "plasmid" in the '270 Patent as "a multicopy plasmid containing the entire nonmutated structural gene coding region for the expression of the complete DNA polymerase I enzyme, which is lethal or debilitating to the growth of the host cell strain when expressed from a multicopy plasmid and has the following three activities: polymerase activity, 5'-3' exonuclease activity, and 3'-5' exonuclease activity." The Court declines to interpret the term "plasmid" as the defendants request.

The '270 Patent claims do not refer to "DNA polymerase I," "Pol I," or the "complete structural gene coding region ... for the expression of DNA polymerase I." Instead, the claims discuss recombinant plasmids "providing for Nick-translation activity," "containing a DNA coding sequence for the expression of Nick-translation activity," and "containing a DNA coding sequence for "the expression of DNA polymerase activity." *See* '270 Patent, claims 1, 11, 14, 17, 32, and 34. The Court will not incorporate the patentees' definition of "DNA polymerase I" and "complete structural gene coding region" in the '708 Patent into the '270 Patent under the guise of interpreting the claim term "plasmid." FN11 The Court therefore adopts the plaintiffs' construction of the '270 Patent.

FN11. The defendants rely heavily on the '270 Patent specification. *See, e.g.,* '270 Patent at col. 1, lines 57-63; id. at col. 2, line 65 to col. 3, line 3; id. at col. 4, lines 4-16. The Court declines to import extraneous limitations from the specification into the patent claims when there are no claim terms to interpret. *See* Du Pont, 849 F.2d at 1433.

CONCLUSION

For the foregoing reasons, the Court hereby construes the '708 and '270 Patent claims as follows:

(1) The term "DNA polymerase I" as used in the claims of the '708 Patent means an enzyme that:

(a) is lethal or debilitating to growth of the host cell strain when expressed from a multicopy plasmid, and

(b) possesses three enzyme activities, namely

(i) polymerase activity,

(ii) 5'-3' exonuclease activity, and

(iii) 3'-5' exonuclease activity.

(2) The phrase "complete structural gene coding region ... for the expression of DNA polymerase I" in claim 1 and the phrase "complete structural gene coding region ... of DNA polymerase I" in claim 25 (and asserted

dependent claims thereto) of the '708 Patent require that the recombinant plasmid have the complete structural gene coding region for the expression of DNA polymerase I. These phrases in the patent claims do not require that the structural gene coding region of the recombinant plasmid be "entire" (i.e., have no missing nucleotide bases) or "non-mutated" (i.e., without a single mutation).

(3) The steps of "excising enzymatically from the DNA molecule the complete structural gene coding region" and "cloning said complete structural gene coding region into a vector plasmid" in claim 25 of the '708 Patent requires only that those two steps be done and does not limit the way in which these steps are to be performed. Claim 25 does not require that the gene coding region be excised from the bacterial source in one piece or inserted into the vector plasmid in one piece.

(4) The phrase "recombinant plasmid providing for nick-translation activity" in claims 1, 11, and 14 of the '270 Patent and the phrase "recombinant plasmid containing a DNA coding sequence for expression of nick-translation activity" in claim 17 of the '270 Patent require that the multicopy plasmids contain a gene coding region for expression of nick-translation activity. The phrase "recombinant plasmid containing a DNA coding sequence for the expression of DNA polymerase activity" in claims 32 and 34 of the '270 Patent requires that the multicopy plasmid contain a gene coding region for the expression of DNA polymerizing activity. There is no basis for reading into these claims the requirements that the plasmids contain a complete structural gene coding region without deletions or mutations, that the DNA polymerase expressed from the plasmid be DNA polymerase I, or that the DNA polymerase I have 3'-5' exonuclease activity and be lethal, debilitating or inhibiting to growth of host cells.

IT IS SO ORDERED.

N.D.Cal.,1997.
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