United States District Court,
D. Massachusetts.

ABBOTT LABORATORIES,
v.
IMCLONE SYSTEMS, INC.

Civil Action No. 07-10216-RGS

May 21, 2008.

Background: Patent owner brought action against competitor alleging infringement of patent that described method of vector construction enhancing expression in eukaryotic cells to enabled commercial production of protein. Court set forth to construe disputed terms.

Holdings: The District Court, Stearns, J., held that:
(1) phrase, "isolated animal cell transfected with a vector," meant cultured cell or cell line derived from animal, which cell or cell line had been transformed or transfected with recombinant nucleic acid that included sequences necessary for its replication in prokaryotic cells;
(2) statements seemingly conclusive on their face in narrowing scope of patented invention fell short of exacting requirements of enforceable disclaimer on closer inspection;
(3) phrase, "selectable marker enzyme," meant enzyme imparting detectable phenotypic property to transfected or transformed cell that could be used to identify which of family of cells had incorporated vector encoding selectable marker enzyme;
(4) conditional statements made during prosecution did not override definition set out in patent specification;
(5) phrase, "blocking element comprising a promoter interposed between the first enhancer and the selectable marker gene, which blocking element selectively attenuates the stimulation of transcription of the selectable marker gene," meant promoter interposed between first enhancer and selectable marker gene that permitted enhancer to stimulate transcription of gene of interest and prevented enhancer from stimulating transcription of selectable marker gene, thereby preventing toxicity associated with enhanced expression of selectable marker enzyme; and
(6) phrase, "expression vector," meant agent, i.e., DNA construct, that could be used to introduce genetic material into cell or organism that directed synthesis of protein that had been encoded by genetic material.

Ordered accordingly.

5,665,578. Construed.

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MEMORANDUM AND ORDER ON CLAIM CONSTRUCTION

STEARNS**, District Judge.**

On February 5, 2007, plaintiff Abbott Laboratories (Abbott) filed this action against defendant Imclone Systems, Inc. (Imclone), alleging infringement of its U.S. Patent No. 5,665,578 (the '578 patent), entitled "Vector and Method for Achieving High Level of Expression in Eukaryotic Cells." A hearing on claim construction was held on May 8, 2008.

BACKGROUND

The '578 patent describes a method of vector construction enhancing expression in eukaryotic cells to enable the commercial production of protein. In the early 1980s, Stephen Gillies and Susumu Tonegawa, two MIT professors, identified certain DNA sequences, called enhancers, which had the potential to dramatically increase the copying of genes. Later, Dr. Gillies discovered that a properly oriented promoter sequence increased production of the protein of interest while blocking the action of the enhancer on other genes in the vector. Abbott was granted the '578 patent for Dr. Gillies's invention in 1997.

The patent has three independent claims (claims 1, 8, and 9). Claim 1 concerns "an isolated animal cell transfected with a vector." Claim 8 concerns "a method of manufacturing an isolated animal cell transfected with a vector." Claim 9 concerns the "expression vector" itself. Each independent claim requires the "vector" or "expression vector" to include a minimum of the following four elements:

(a) "a selectable marker gene comprising a promoter operatively linked to a nucleic acid encoding a selectable marker enzyme;"

(b) "a transcription unit comprising a promoter operatively linked to a nucleic acid encoding a protein;"

(c) "an enhancer located between the selectable marker gene and the transcription unit, which enhancer stimulates transcription of both the selectable marker gene and the transcription unit compared to the transcription of both the selectable marker gene and the transcription unit in the absence of the enhancer;"

(d) "a blocking element comprising a promoter interposed between the enhancer and the selectable marker gene, which blocking element selectively attenuates the stimulation of transcription of the selectable marker gene."

CLAIM CONSTRUCTION

[1] [2] [3] [4] [5] "It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed.Cir.2005) (internal quotations and citation omitted). Claim construction, while not devoid of factual considerations, is primarily a question of law for the determination of the court. *See* Markman v. Westview Instruments, Inc., 517 U.S. 370, 388-389, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). In performing this task, the court ideally limits itself to the construction of only those terms "that are in controversy, and only to the extent necessary to resolve the controversy." Vivid Techs., Inc. v. American Sci. & Eng'g, Inc., 200 F.3d 795, 803 (Fed.Cir.1999). A disputed term must be given the meaning that it would have had to a person of ordinary skill in the relevant art at the time of the invention. *See* Phillips, 415 F.3d at 1313. The court "indulge[s] a heavy presumption that claim terms carry their full and ordinary customary meaning unless the patentee unequivocally imparted a novel meaning to those terms or expressly relinquished claim scope during prosecution." Omega Eng'g, Inc. v. Raytek Corp., 334 F.3d 1314, 1323 (Fed.Cir.2003) (internal citations omitted).

[6] [7] [8] A disputed term should be construed by first examining the intrinsic evidence of record, that is, the words of the claims themselves, the specification, and the prosecution history. *See* Phillips, 415 F.3d at 1314. The patent specification " 'is always relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term.' " Id. at 1315, quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996) "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention [in the specification] will be, in the end, the correct construction." Id. at 1316.

1. Disputed Terms

The parties ask the court to construe four terms.

A. "*isolated animal cell transfected with a vector*"

[9] According to Abbott, the plain and ordinary meaning of the term is: "a culturedcell or cell line derived from an animal, which cell or cell line has been transformed or transfected with recombinant nucleic acid that includes sequences necessary for its replication in prokaryotic cells." The Abbot construction finds support in the specification, which references the transfection of vectors "into selected, preferably continuous, animal cell lines to obtain continuously culturable transformants characterized by a high level of expression of the protein of interest." *See* '578 patent, col. 4, ll. 5-9.

Imclone does not disagree. Instead, it argues that during prosecution of the patent, Abbott disclaimed cells containing a high copy number of the transfected vector DNA in order to avoid prior art. Accordingly, Imclone contends that the term should be construed as: "an isolated animal cell into which *a low copy number* of foreign DNA has been introduced through the use of a vector." (Emphasis added). There is no reference to copy number in the specification.

[10] [11] [12] Although the words of the claims best define the scope of the patented invention, statements made during prosecution may also affect the scope of the claims. *See* Computer Docking Station Corp. v. Dell, Inc., 519 F.3d 1366, 1374 (Fed.Cir.2008). *Cf.* Phillips, 415 F.3d at 1317 ("[B]ecause the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes."). To influence the interpretation of what is otherwise the plain meaning of a claim, a statement culled from the prosecution history must be a "clear and unmistakable disavowal of scope." Computer

Docking, 519 F.3d at 1374, citing Purdue Pharma L.P. v. Endo Pharms. Inc., 438 F.3d 1123, 1136 (Fed.Cir.2006). "A patentee could do so, for example, by clearly characterizing the invention in a way to try to overcome rejections based on prior art." Computer Docking, 519 F.3d at 1374. The disclaimer doctrine "protects the public's reliance on definitive statements made during prosecution by precluding patentees from recapturing through claim interpretation specific meanings clearly and unmistakably disclaimed during prosecution." Id. at 1374-1375. FN1 It follows that ambiguous statements are not enough to trigger the doctrine. For example, prosecution disclaimer does not apply "if the applicant simply describes features of the prior art and does not distinguish the claimed invention based on those features." Id. at 1375.

FN1. Imclone argues that this case is indistinguishable from Computer Docking, where the Federal Circuit affirmed the district court's rejection of the patentee's claim that the term "portable computer" encompassed a laptop computer, holding that the term was properly construed as meaning "a computer without a built-in display or keyboard that is capable of being moved or carried about." The Federal Circuit agreed with the district court that while ordinarily the plain meaning of the term "portable computer" would require the computer to be "capable of being moved about" (which would include a laptop computer), the patentee's prosecution-related statements clearly and unmistakably distinguished the claimed invention from a laptop. Accordingly, a narrower construction was required.

[13] During prosecution of the '578 patent, in a November 10, 1994 Office Action, the PTO examiner rejected the claims because:

[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to alter the vectors taught by either Gillies et al. (A) or Gillies et al. (AR") [sic] by inserting a promoter between the selectable marker promoter and the enhancer for the purpose of decreasing the expression of the selectable marker as taught by deVilliers et al. The motivation for this genetic alteration is taught by Kawasaki et al.; decreasing the expression of the selectable marker increases the copy number of the plasmids containing a cloned foreign gene, thereby resulting in an increase in the production of the protein product encoded by the foreign gene.

Imclone's Ex. F at 6-7.

In response, Abbott filed a Request for Reconsideration on January 28, 1997 (Paper No. 57). *See* Imclone's Supp. Ex. F. Imclone identifies three prosecution statements made by Abbott in Paper No. 57 that it contends narrowed the scope of Dr. Gillies's invention. In each of these statements, Abbott indicated that a high copy number might have the inimical effect of raising the toxicity of the marker enzyme to an unmanageable level. The statements are: (1) "Applicant's claimed invention does *not* provide cells with increased copy number plasmids." Id. at 13 (emphasis in original); (2) "[C]ontrary to Kawasaki et al., a *low* copy number is desirable to Applicant's invention, since an increase in copy number would undesirably increase the number of wild type marker genes and the levels of the wild type marker protein and defeat the purpose of the Applicant's invention." Id. (emphasis in original); and (3) "[T]he prior art ... does not suggest that the insertion of a blocking element ... will result in the enhanced selection of transformants that synthesize very high, commercially valuable, levels of a protein of interest, yet maintain a low vector copy number and non-toxic, unenhanced levels of marker gene product." Id. at 18.

[14] While on their face, these statements seem conclusive, on closer inspection they fall short of the exacting requirements of an enforceable disclaimer. As an initial matter, it is not clear whether the

statements relate to the meaning of the claims language or are meant to explain the workings of the invention. Assuming that the statements do concern the claim elements, they can be read reasonably as supporting either party's proffered construction. The entire prosecution record reveals a conflicting history regarding copy number. In another portion of Paper No. 57 not cited by Imclone, Dr. Gillies clearly stated that the "system *does not* depend upon copy number." Id. at 13 (emphasis in original). In earlier statements, he declared that the invention worked "irrespective [of] whether multiple copies of the plasmid have or have not been taken up." Response to Office Action dated October 6, 1988 (Abbott's Ex. F at 3); *see also* id. at 3-4 ("[C]lones produced in accordance with the invention often have comparable gene copy numbers to clones produced using conventional vectors. However, that fact has no direct relevance to the mechanism of action of the invention."). Disclaimer does not apply where the statements in the prosecution history are subject to competing reasonable interpretations, *see* SanDisk Corp. v. Memorex Prods., Inc., 415 F.3d 1278, 1287 (Fed.Cir.2005), especially when as here, one of the reasonable interpretations aligns with the plain and ordinary meaning of the disputed term. Id., citing Golight, Inc. v. Wal-Mart Stores, Inc., 355 F.3d 1327, 1332 (Fed.Cir.2004). FN2

FN2. The second of the statements cited by Imclone, (which comes closest to a "clear and unmistakable" disavowal) is limited explicitly to "wild type" marker genes.

The court will adopt Abbott's construction.

B. "*selectable marker enzyme*"

[15] Abbott describes a "selectable marker enzyme" as: "an enzyme imparting to a transfected or transformed cell a detectable phenotypic property that can be used to identify which of a family of cells have incorporated the vector encoding the selectable marker enzyme." The specification defines "selectable marker enzyme" by reference to the genes expressing the desired enzyme; "The vectors of the invention may exploit various marker genes which impart to a successfully transfected cell a detectable phenotypic property which can be used to identify which of a family of cells have successfully incorporated the recombinant DNA of the vector." *See* '578 patent, col. 4, ll. 34-38.

[16] Imclone argues that Abbott's construction ignores the purpose of the invention and descriptive statements that Abbott made during prosecution. In Imclone's view, both the specification and the prosecution history demonstrate that the invention was intended to prevent toxicity by suppressing transcription of the selectable marker gene. Imclone cites to a number of statements purporting to show that Abbott distinguished the prior art based on the prevention of marker toxicity. Accordingly, Imclone offers the construction: "an enzyme that enables a transfected cell to survive in a toxic selection medium and which, if expressed at enhanced levels, is toxic or lethal to the transfected cell." However, the statements upon which Imclone relies in support of its suggested limitation are written in permissive terms: "too high a level of the marker protein *may* interfere with the cell's metabolism"; "overproduction of a marker gene product *might* undesirably cause intracellular toxicity." (emphasis added). These conditional statements do not override the definition set out in the specification, nor would they have been understood by one skilled in the art as having any other than a cautionary import.

The court will adopt Abbott's proposed construction.

C. "*blocking element comprising a promoter interposed between the first enhancer and the selectable*

marker gene, which blocking element selectively attenuates the stimulation of transcription of the selectable marker gene" FN3

FN3. For convenience, the parties refer to this disputed term as the "blocking element."

[17] This is the most vigorously disputed term. Abbott submits the following construction: "a promoter sequence on which the enhancer acts disposed in the vector according to the teachings of the patent so as to be expected to selectively interfere with enhanced transcription of the selectable marker gene." The omission is glaring: Abbott's proposed construction effectively neuters the phrase "selectively attenuates" by substituting the circumlocution "so as to be expected to selectively interfere."

Imclone offers an even wordier construction: "a promoter interposed between the first enhancer and the selectable marker gene that must, without increasing copy number, permit the enhancer to stimulate transcription of the gene of interest and prevent the enhancer from stimulating transcription of the selectable marker gene, thereby preventing toxicity associated with enhanced expression of the selectable marker enzyme." Imclone's proposed construction bootlegs the "without increasing copy number" from its proposed construction of the "isolated animal cell" term.

There are three main differences between the competing constructions: (1) whether the blocking element must preventthe enhancer from stimulating transcription of the selectable marker gene; FN4 (2) whether the blocking element must prevent any toxicity associated with enhanced expression of the selectable marker gene; and (3) whether the blocking element must also not precipitate an increase in copy number.

FN4. In other words, whether the "blocking element" is a means-plus-function term.

As to the first issue, the specification clearly teaches that the blocking element is intended to suppress the stimulation of transcription. *See* '578 patent, col. 7, ll. 1-5 ("The vectors of the invention accordingly include a blocking element interposed between the enhancer and the transcription unit comprising the marker region such that transcription of the marker region gene is not enhanced."). *See also* id., col. 2, ll. 14-20 ("The invention features expression vectors constructed such that the cellular enhancer ... is active to promote high levels of expression of a desired gene encoding a protein product, but does not significantly affect the level of expression of the marker protein."). The specification explains that "[t]he approach of the invention is to interpose between the cellular enhancer and the transcription unit encoding the marker protein a DNA comprising nucleotides *having the function of blocking the stimulating effect of the enhancer element on the marker gene*." *See* '578 patent, col. 2, ll. 22-26 (emphasis added). During prosecution, Abbott distinguished the invention by stating that it was not simply a DNA sequence, but a DNA sequence that performs a specific function. *See, e.g.,* Mar. 15, 1989 Office Action (Imclone's Ex. J at 2) ("The difference between what is claimed in [the '281 patent] and that claimed in the instant application is *use of a blocking element to attenuate* increased expression of the selectable marker.") (emphasis added). Accordingly, Abbott's effort to strip the blocking element of any function necessarily fails.

As to the second issue, the blocking element also solves the problem of toxicity associated with the enhanced expression of the selectable marker enzyme.

Thus, while the enhancer increases expression of both the marker gene and the gene of interest, when the

marker gene encodes an ezyme that enables cell survival in a toxic medium, the selection procedure may eliminate transformants expressing very high levels of the marker protein, thereby precluding the isolation of transformants expressing very high levels of the protein of interest. The way to overcome the foregoing problem is based on the discovery that the stimulating effect of the enhancer element is dissipated on a promoter, irrespective of its orientation, and whether or not the promoter is present together with a gene. The vectors of the invention accordingly include a blocking element interposed between the enhancer and the transcription unit comprising the marker region such that transcription of the marker region is not enhanced. Use of such vectors inherently enables the isolation of transformants which produce the marker protein at relatively low but detectable levels, levels sufficient to confer viability, yet display enhanced, high level transcription of the gene encoding a protein product. Thus, the level of expression of the protein of interest relative to that of the marker protein will increase when enhancement of the marker protein is blocked.

See '578 patent, col. 6, l. 55-col. 7, l. 13. Abbott made similar statements throughout the prosecution history in order to avoid prior art. *See, e.g.,* Apr. 14, 1992 Response to Office Action (Imclone's Ex. L at 7) ("Applicant has utilized these known components to formulate the invention, i.e., that for a desired expression/selection system, expression of the expressible gene may be enhanced without coordinately enhancing expression of the marker gene, and thus avoiding unnecessary marker gene product toxicity to the host cell."). *See also* Aug. 22, 1995 Response to Office Action (Imclone's Ex. M at 4) ("If the blocking element were absent, such that transcription of both the marker gene and the gene of interest were enhanced, the transformed cell would succumb to the intracellular toxic effects of the expressed marker gene product."); id. at 6 ("More pointedly, Kawasaki et al. does not teach or suggest that *overproduction* of a marker gene product might undesirably cause intracellular toxicity.") (emphasis in original).

The third issue closely tracks the argument made by the parties in construing the "isolated animal cell" term. Imclone asserts that Abbott made statements during prosecution that the blocking element must not cause an increase in copy number. *See, supra*. For the reasons stated above, those statements are too ambiguous to constitute a surrender of the plain meaning of the affected claim.

The court will partially adopt Imclone's construction and define the blocking element as: "a promoter interposed between the first enhancer and the selectable marker gene that permits the enhancer to stimulate transcription of the gene of interest and prevents the enhancer from stimulating transcription of the selectable marker gene, thereby preventing toxicity associated with enhanced expression of the selectable marker enzyme."

D. "*expression vector*"

[18] Abbott contends that the term is well established in the art and means: "a vector that directs the production (i.e., transcription and translation) of a protein encoded by a portion of the DNA sequence of the vector." Imclone argues that Abbott's construction ignores the usage of the term "vector" in the specification and the patent claims as describing a carrier of foreign DNA into a cell, as opposed to a component of the cell itself. The dispute here is over claim scope. Imclone disputes whether the expression vector reads on cells that have been transformed by transfection. In Imclone's view, it does not. The court agrees. The terms "vector" and "expression vector" are used interchangeably throughout the patent. The claims clearly distinguish the term "vector," which is described in the claim as an agent used for transfection, from the "isolated animal cells" that are the product of that transfection. Claim 1's recitation of an "an isolated animal cell transfected with a vector" confirms that the vector described and claimed in the patent is an agent that is

used to transfect (i.e., introduce DNA into) a cell.

The court will adopt Imclone's construction: "an agent (i.e., a DNA construct) that can be used to introduce into a cell or organism genetic material that directs the synthesis of a protein that is encoded by the genetic material."

ORDER

For the foregoing reasons, the disputed terms are construed as follows:

1. "isolated animal cell transfected with a vector" means "a cultured cell or cell line derived from an animal, which cell or cell line has been transformed or transfected with recombinant nucleic acid that includes sequences necessary for its replication in prokaryotic cells."

2. "selectable marker enzyme" is "an enzyme imparting to a transfected or transformed cell a detectable phenotypic property that can be used to identify which of a family of cells have incorporated the vector encoding the selectable marker enzyme."

3. "blocking element comprising a promoter interposed between the first enhancer and the selectable marker gene, which blocking element selectively attenuates the stimulation of transcription of the selectable marker gene" means "a promoter interposed between the first enhancer and the selectable marker gene that permits the enhancer to stimulate transcription of the gene of interest and prevents the enhancer from stimulating transcription of the selectable marker gene, thereby preventing toxicity associated with enhanced expression of the selectable marker enzyme."

4. "expression vector" means "an agent (i.e., a DNA construct) that can be used to introduce into a cell or organism genetic material that directs the synthesis of a protein that is encoded by the genetic material."

SO ORDERED.

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