United States Court of Appeals for the Federal Circuit

00-1223, -1267

BIO-TECHNOLOGY GENERAL CORP.,

Plaintiff/Counterclaim Defendant-Cross Appellant,

and

BIO-TECHNOLOGY GENERAL (ISRAEL) LTD.,

Counterclaim Defendant-Cross Appellant.

v.

GENENTECH, INC.,

Defendant/Counterclaimant-Appellant.

Richard L. DeLucia, Kenyon & Kenyon, of New York, New York, argued for plaintiff/counterclaim defendants-cross-appellants. With him on the brief were Thomas J. Meloro, Charles A. Weiss, and William G. James, II.

Leora Ben-Ami, Clifford Chance Rogers & Wells LLP, of New York, New York, argued for defendant/counterclaimant-appellant. With him on the brief was John E. Kidd. Of counsel were Roy E. Hofer, Cynthia A. Homan, and Meredith Martin Addy, Brinks Hofer Gilson & Lione, P.C., of Chicago, Illinois.

Appealed from: United States District Court for the Southern District of New York

Chief Judge Thomas P. Griesa

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v.

GENENTECH, INC.,

Defendant/Counterclaim-Appellant.

DECIDED: September 27, 2001

Before NEWMAN, CLEVENGER, and GAJARSA, Circuit Judges.

NEWMAN, Circuit Judge.

Genentech, Inc. appeals the decision of the United States District Court for the Southern District of New York, entering judgment as a matter of law that claim 2 of United States Patent No. 4,601,980, issued July 22, 1986, is invalid for lack of enablement. Bio-Technology Gen. Corp. v. Genentech, Inc., No. 95-Civ-0110-TPG (S.D.N.Y. February 18, 2000). We reverse the judgment of invalidity and remand for further proceedings with respect to infringement.

Bio-Technology General cross-appeals the district court's dismissal of the antitrust counts. Bio-Technology Gen. Corp. v. Genentech, Inc., 886 F. Supp. 377, 36 USPQ2d 1169 (S.D.N.Y. 1995). This action is affirmed.

BACKGROUND

The '980 patent is directed to a method of producing human growth hormone (hGH) using the recombinant techniques of bacterial reproduction and gene expression, as summarized in this court's prior decision in this action, Bio-Technology Gen. Corp. v. Genentech, Inc., 80 F.3d 1553, 38 USPQ2d 1321 (Fed. Cir. 1996) (BTG I) (affirming grant of preliminary injunction).[Fn 1]

In its naturally occurring active form, the human growth hormone (hGH) is a

protein molecule consisting of 191 specific amino acid molecules in precise sequence. Prior attempts at the recombinant production of hGH in quantities adequate for medicinal treatment had produced an inactive product consisting of the 191 amino acids attached to an inactivating leader sequence of additional amino acids. In the search for a method for producing biologically active hGH, Genentech developed a complex chemical and biological process whereby the inactivating leader sequence is replaced with the amino acid methionine, to produce an active hGH having 192 amino acids.

In brief summary, the complementary DNA (cDNA) of the hGH gene, which includes the codons[Fn 2] for the naturally occurring leader sequence, was obtained by reverse transcription of messenger RNA isolated from pituitary cells. The cDNA was then treated with a restriction enzyme to remove the portion corresponding to the leader sequence plus the first 23 codons of the hGH gene, leaving a cDNA segment of codons corresponding to amino acids 24-191 of the hGH protein. A second DNA fragment that had been chemically synthesized, consisting of a "start" codon encoding the amino acid methionine plus the first 23 codons of the hGH gene, was chemically ligated to the segment containing codons 24-191. The product was a "semi-synthetic gene" consisting of a single strand of DNA containing 192 codons: the codon for methionine plus the 191 codons for naturally occurring hGH.

This strand of DNA was subjected to recombinant techniques using the bacterium *E. coli*, whereby the bacterial cell reproduces the semi-synthetic gene which in turn produces, by the mechanisms of "gene expression," the corresponding 192 amino acid protein molecule. This protein consists of the 191 amino acid naturally occurring hGH (called "mature hGH") with the attached leader amino acid

methionine; this methionine-containing hGH is called "met-hGH." The '980 patent states that "one can expect" the methionine to be cleaved within the bacterial cell, and that "in any event" the methionine leader does not affect the bioactivity of the expression product:

> [T]he expression product will in every case commence with the amino acid coded by the translation start signal (in the case of ATG, f-methionine). One can expect this to be removed intracellularly, or in any event to leave the bioactivity of the ultimate product essentially unaffected.

'980 patent, col. 7, lines 51-57. It is not disputed that mature hGH and met-hGH are biologically equivalent.

ENABLEMENT

The principal issue on appeal is whether the '980 patent is invalid for lack of enablement in terms of 35 U.S.C. §112. [Fn 3] Claim 2 of the '980 patent, the only claim in suit, is as follows:

> 2. A method for producing human growth hormone which method comprises culturing bacterial transformants containing recombinant plasmids which will, in a transformant bacterium, express a gene for human growth hormone unaccompanied by the leader sequence of human growth hormone or other extraneous protein bound thereto, and isolating and purifying said expressed human growth hormone.

BTG argues that the method of the '980 patent produces only met-hGH, and because the leader methionine may not be cleaved intracellularly by the *E. coli* (or if cleavage occurs, such cleavage will not produce a "substantial amount" of mature hGH), claim 2 is invalid for failure to enable the production of mature hGH. Genentech responds that the invention of claim 2 is enabled by the production of met-hGH, and that in any event it suffices if the '980 process produces any amount of mature hGH along with the met-hGH.

Claim 2 has been construed in other litigation. In Novo Nordisk of North America,

Inc. v. Genentech, Inc., 77 F.3d 1364, 1371, 37 USPQ2d 1773, 1779 (Fed. Cir. 1996) the court, holding that "properly construed, claim 2 is a process for the direct expression of met-hGH or hGH," vacated a preliminary injunction for a process that was not a direct expression of hGH or met-hGH. In BTG I, an interlocutory appeal in this action, this court again construed claim 2 and ruled that "the production of hGH must also be considered to be within the literal scope of claim 2." 80 F.3d at 1560, 38 USPQ2d at 1326. This construction binds us.

At the trial, both sides presented extensive expert testimony and attorney argument on the issue of enablement. The district court submitted the following two questions to the jury:

> 1. Has BTG proven by clear and convincing evidence that the '980 patent did not enable a scientist skilled in the art in July 1979 to make any mature human growth hormone of 191 amino acids?
>
> 2. Has BTG proven by clear and convincing evidence that the '980 patent did not enable a scientist skilled in the art in July 1979 to make a substantial amount of mature human growth hormone of 191 amino acids? [The jury was instructed that "a substantial amount" means "principally," "mainly," or "almost entirely."]

The jury answered "NO" to question 1 and "YES" to question 2.

After discharging the jury, the district court granted BTG's motion for judgment as a matter of law as to question 1, stating that "no reasonable jury could have failed to answer 'YES' to question 1." The court stated that on Genentech's "conten[tion] that the 191 product is covered . . . this patent must enable the production of 191." The court stated that the position that mature hGH was enabled by the '980 patent was contrary to Genentech's "string of conclusive, unambiguous admissions, representations to the patent office, etc., [and] representations in testimony that this '980 patent produced met-hGH and nothing else." The court entered judgment that claim 2 was invalid for lack of enablement

of hGH of 191 amino acids.

A

Enablement is a matter of law based on underlying factual inquiries. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1369, 52 USPQ2d 1129, 1134 (Fed. Cir. 1999). We give plenary review to the grant of judgment as a matter of law, applying the same standard to review of the evidence as did the district court; thus we must ascertain whether there was substantial evidence presented at the trial to support the findings necessary to the jury's verdict. Loral Fairchild Corp. v. Sony Corp., 181 F.3d 1313, 1320, 50 USPQ2d 1865, 1869 (Fed. Cir. 1999); Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1571, 1 USPQ2d 1081, 1085 (Fed. Cir. 1986). The evidence presented at trial must be considered in the light most favorable to the jury's verdict, drawing reasonable factual inferences and resolving issues of credibility in favor of the verdict. See Hebert v. Lisle Corp., 99 F.3d 1109, 1114-15, 40 USPQ2d 1611, 1614 (Fed. Cir. 1996) ("When an ultimate question of law or fact is decided by the jury, on review it is assumed that the jury resolved the evidentiary facts as appropriate to support the verdict.").

Genentech states that the district court improperly substituted its view of the evidence for that of the jury, and that when the evidence is viewed in the light most favorable to the verdict, the jury's "NO" answer to question 1 is supported by substantial evidence. Genentech points to the extensive expert testimony that the process of the '980 patent enables the production of some mature hGH, and stresses that BTG itself provided such evidence in a New Drug Application to the Food and Drug Administration stating that hGH made by the process of the '980 patent contains 93.8% met-hGH and 6.2% mature hGH.

The jury received conflicting expert opinion on this issue. Dr. Steven Hughes of the National Cancer Institute, testifying as an expert on behalf of Genentech, explained that the '980 patent shows a process wherein the initial gene expression product is met-hGH, and some of the methionine may be removed intracellularly to produce mature hGH. Dr. Hughes explained that the BTG process similarly uses a methionine start codon, that the expression product is met-hGH of 192 amino acids, and that

> about 6.2% of the met is removed intracellularly and the other 93.8% of the met stays on, so there is a mixture of met-hGH and met-less hGH in this material, and . . . certainly the majority of the protein is met-hGH, but there is enough met-less that you can easily see it.

Professor James Manley of Columbia University also testified as an expert. He stated that the processes described in the '980 patent and in BTG's New Drug Application are "remarkably similar," that both initially produce met-hGH, and that intracellular cleavage "almost certainly" produced the 6.2% mature hGH reported by BTG. Nobel laureate Sidney Altman of Yale University also testified on behalf of Genentech. Professor Altman agreed with Dr. Hughes and Professor Manley, and stated that at the time of filing of the '980 patent one of skill in this field would be able to "use the '980 process and separate out from that mature human growth hormone to treat children."

Opposing Genentech's version of the scientific facts, BTG presented expert testimony that the 6.2% mature hGH in the BTG product came from extracellular processing of the met-hGH. BTG did not dispute that its process used a methionine leader and recombinant procedures as in the '980 patent. Instead, the thrust of BTG's argument was that Genentech did not obtain any mature hGH by intracellular cleavage of the methionine, BTG pointing for support to Genentech's

research records and patent documents. BTG asserted that in the absence of evidence that mature hGH was actually produced using the '980 process, the patent is invalid. BTG also argued that the product that BTG submitted to the FDA in 1995 can not serve to establish that such a product was enabled in 1979 when the '980 application was filed.

Extensive testimony and argument was presented by both sides. Although the issues are not matters of common experience, the witnesses for both sides testified with clarity, and did not differ significantly in their statements concerning the underlying science; they differed in the inferences drawn at the edges where there was not sufficient evidence or knowledge for scientific certainty. For example, they discussed intracellular cleavage of the methionine, and disputed the effects of the asserted differences between the Genentech and the BTG procedures. Thus the trial testimony showed reasonable scientists differing as to whether mature hGH could be produced by intracellular cleavage in recombinant procedures. The weighing of conflicting evidence is a jury function. See Al?Site Corp. v. VSI International Inc., 174 F.3d 1308, 1317, 50 USPQ2d 1161, 1165 (Fed. Cir. 1999) ("As the finder of fact, the jury receives deference for its function of weighing witness demeanor, credibility, and meaning.")

When scientific certainty is not available, and the scientific theories and evidence are within a reasonable range of difference of scientific opinion, resolution of such difference based on weight and credibility of evidence is the province of the trier of fact. See Comark Communications, Inc. v. Harris Corp., 156 F.3d 1182, 1189, 48 USPQ2d 1001, 1008 (Fed. Cir. 1998) ("It is not the function of this court to reweigh the evidence presented to the jury."). On the record before the jury, the jury verdicts as to both question 1 and question 2 were supported by substantial

evidence and could have been reached by a reasonable jury. The district court's grant of judgment as a matter of law as to question 1 is vacated, and the jury verdict is reinstated.

B

BTG argues that the jury's answer to question 2, that the '980 patent did not enable "a substantial amount" of mature human growth hormone, is determinative as to enablement, whatever the answer to question 1. Since it is not necessary to our decision, we have not reviewed the answer to question 2, or the correctness of the jury instruction defining "substantial amount."

C

Claim 2, according to BTG, requires "the production of 'principally or mainly' mature hGH (allowing for the presence of smaller amounts of met?hGH if the cleavage is not complete)." Thus BTG argues that claim 2 is not enabled by the '980 patent, even if that method is deemed to yield as much mature hGH as the 6% reported by BTG. BTG's position is contrary to the claim construction that is the law of this case. This court held that claim 2 "encompass[es] both met-hGH and hGH." Novo Nordisk, 77 F.3d at 1369, 37 USPQ2d at 1777. This construction does not require that mature hGH is directly expressed, or produced in substantial amount or to the exclusion of met-hGH, as BTG argues. Genentech explained at trial, and the witnesses for both sides agreed, that the product of the gene expression is met-hGH, and that any mature hGH results from the cleavage of the methionine from the expression product.

BTG also argues that Genentech is estopped from asserting that the '980 patent enables the production of any mature hGH whatsoever, pointing to Genentech's statements to the PTO, in prosecuting a divisional application leading to U.S.

Patent No. 4,658,021, that the methionine is not cleaved intracellularly. That application cited a scientific article published by Genentech in Nature 293, 408 (1981), which stated that "[t]he bacterially synthesized hGH, produced from *E. coli*, is methionyl-hGH . . . the extra methionine arising from the AUG start codon inserted at the beginning of the gene." These arguments do not establish BTG's position that its process is removed from the enabled scope of the '980 patent because it produces some mature hGH; that position was rejected in BTG I and Novo Nordisk.

Genentech does not dispute that the expression product of the method shown in the '980 patent is met-hGH. Instead, Genentech argues that this does not exclude the formation of some mature hGH through intracellular cleavage, referring, inter alia, to its United States Patent No. 4,755,465, which was pending before the same examiner as the application issuing as the '980 patent. The '465 specification states that "the hGH obtained using the process of United States Patent No. 4,342,832 [having the same specification as the '980 patent] contains at least a substantial amount of hGH to which the amino acid methionine not found in native hGH is appended at the N-terminal end of the protein." Col. 1, lines 38-42. Thus Genentech states that the examiner understood that the dominant product of the claimed method is met-hGH, but that mature hGH is not excluded from production.

Claim 2, read in light of the specification, neither requires nor excludes intracellular cleavage to remove the methionine. The fact that the '980 patent produces met-hGH, or at most small amounts of mature hGH, does not invalidate the claims for lack of enablement. The court in BTG I set no requirement that the methionine must be cleaved. Thus it was incorrect to hold claim 2 invalid on the

ground that the product of the procedures of the '980 patent was met-hGH. The district court's judgment of invalidity is reversed.

INFRINGEMENT

In describing Genentech's position that "it should be able to sue for infringement anyone who violates, anyone who infringes the patent with respect to 191," the district court apparently viewed this position as overreaching. Notably, BTG I did not suggest that claim 2 of the '980 patent would cover all methods for producing mature hGH. See Novo Nordisk, 77 F.3d at 1369-70, 37 USPQ2d at 1777-78 (rejecting infringement where hGH was made by a different process).

The only description of BTG's product to which we have been directed is BTG's NDA which describes the product as 93.8% met-hGH and 6.2% mature hGH. The district court did not decide the question of infringement. In its appeal brief Genentech states that BTG conceded infringement if the '980 patent were valid, and BTG responds that it made no such concession. The record is ambiguous as to the existence of such a concession, and the parties do not provide enlightenment. We remand to the district court for resolution of the question of infringement.

THE CROSS APPEAL

A

BTG's declaratory complaint, filed in January 1995, included an antitrust claim under Handgards Inc. v. Ethicon Inc., 601 F.2d 986, 202 USPQ 342 (9th Cir. 1979), and various state law tort claims. BTG's argument was that Genentech's infringement suit against BTG in Delaware and an action seeking exclusion by the International Trade Commission were "sham litigation" based on patents that Genentech knew were invalid and not infringed. The district court dismissed these

claims under Fed. R. Civ. P. 12(b)(6).

BTG states that the dismissal was improper because the district court relied on the findings in an Initial Determination of an administrative law judge in the ITC proceeding. BTG states that the ALJ's findings were neither reviewed nor adopted by the Commission because Genentech's complaint was dismissed for discovery abuse, and thus can not serve as a basis for dismissal of the antitrust counts. Genentech responds that the district court did not rely blindly on the ALJ's findings, but reviewed the lengthy record of the ITC trial. The district court, concluding that the ITC action was not sham litigation, explained:

> The ITC found (1) based on defendant Genentech's complaint that sufficient bases existed for the ITC to commence an investigation against plaintiff for infringement of these patents; (2) the ALJ denied no less than six motions for summary determination, five attacking the substance of defendant's patents; and (3) the ALJ ultimately held (although based on an incomplete record) that plaintiff was infringing defendant's '980 and '832 patents. Therefore, defendant's ITC proceeding can in no way be termed objectively baseless because the facts speak loudly to the contrary. As a result, defendant has Noerr?Pennington immunity and plaintiff's antitrust cause of action based upon Handgards allegations must fail and be dismissed.

BTG v. Genentech, 886 F. Supp. at 382, 36 USPQ2d at 1173.

We do not discern reversible error in the district court's ruling. Although BTG is correct that the ALJ's Initial Determination is not a final decision and receives no deference, the record of the ITC proceeding was subject to review by the district court on the issue of whether the litigation was baseless. Other than to object to the court's recourse to the ITC record, BTG does not argue the propriety of the dismissal. We conclude that the dismissal of the Handgards claim based on Noerr-Pennington immunity was correct.

B

BTG also contends that the district court abused its discretion in not granting BTG's request

in December 1998 to file a second amended antitrust complaint, on theories based on Handgards and on Walker Process Equipment, Inc. v. Food Machinery & Chemical Corp., 382 U.S. 172, 147 USPQ 404 (1965). Genentech opposed the filing on grounds of futility, substantial delay, and law of the case.

BTG states that these are new antitrust issues, different from those that were previously dismissed. Genentech responds that BTG told the district court that "the antitrust claims in the Second Amended Complaint arose from the same conduct, transactions and occurrences as in the originally filed complaint," quoting BTG's brief to the district court. BTG does not mention, in its brief before us, when it learned of these asserted new violations, or explain how the district court erred other than to argue that "leave to amend is 'freely given.'" The Second Circuit has observed that "considerations of undue delay, bad faith, and prejudice to the opposing party [are] touchstones of a district court's discretionary authority to deny leave to amend." Barrows v. Forest Labs., 742 F.2d 54, 58 (2d. Cir 1984). We have not been presented with sufficient reason to overturn this discretionary decision.

The denial of leave to file a second amended complaint is affirmed.

C

BTG also cross-appeals the district court's dismissal, by directed verdict, of BTG's contention that the term "a gene" in claim 2 is not enabled and thus invalidates the claim. Genentech states that BTG withdrew that issue at trial; BTG states it did not. We conclude that BTG did not waive all right of appeal of this ruling.

BTG's position is that Genentech's amendment changing "the gene" to "a gene" rendered claim 2 non-enabled because in 1979 it was not reasonably feasible to synthesize an entire gene coding for human growth hormone. BTG argues that "a gene" must be construed to cover all possible synthetic codon sequences that could produce the 191-amino acid hGH, a

number that BTG states is on the order of 3^{191} or 3^{192}. Thus BTG argues that the full scope of "a gene" was not enabled as a matter of law.

This question, although interesting, is not relevant. The premise on which BTG relies is not developed, and the BTG product here charged with infringement is not asserted to be based on a hypothetical non-enabled codon sequence. Speculative construction of a claim term is not grounds for invalidation based on nonenablement of the speculative construction. The district court correctly dismissed this issue.

CONCLUSIONS

The judgment that claim 2 of the '980 patent is invalid on the ground of non-enablement is reversed. We remand for further proceedings with respect to the issue of infringement.

The dismissal of BTG's antitrust claim and denial of leave to file the second amended complaint is affirmed.

In view of these conclusions, the preliminary injunction is reinstated.

REVERSED IN PART; AFFIRMED IN PART; REMANDED

INJUNCTION REINSTATED

[Fn 1] For a general discussion of recombinant technology and gene expression, see In re O'Farrell, 853 F.2d 894, 895?99, 7 USPQ2d 1673, 1674?77 (Fed. Cir. 1988). Other background information can be found in, for example, Watson, Tooze, & Kurtz, Recombinant DNA: A Short Course (1983).

[Fn 2] A codon is a sequential grouping of three nucleotides, selected from the four nucleotide bases adenine, guanine, cytosine, and thymine. Each codon codes for a specific amino acid.

[Fn 3] 35 U.S.C. §112 ¶1 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 . . . .

BACK