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United States Court of Appeals for the Federal Circuit

02-1312

GENZYME CORPORATION
and MOUNT SINAI SCHOOL OF MEDICINE OF NEW YORK UNIVERSITY,

Plaintiffs-Appellants,

v.

TRANSKARYOTIC THERAPIES, INC.,

Defendant-Appellee.

Laura A. Coruzzi, Pennie & Edmonds LLP, of New York, New York, argued for plaintiffs-appellants. With her on the brief were Stephen S. Rabinowitz. Of counsel on the brief were Stanton T. Lawrence, III and Todd A. Wagner, Arnold & Porter, of Washington, DC.

Leora Ben-Ami, Clifford Chance Rogers & Wells LLP, of New York, New York, argued for defendant-appellee. With her on the brief were Patricia A. Carson and Vladimir Drozdoff.

Appealed from: United States District Court for the District of Delaware

Judge Gregory M. Sleet

United States Court of Appeals for the Federal Circuit

02-1312

GENZYME CORPORATION
and MOUNT SINAI SCHOOL OF MEDICINE OF NEW YORK UNIVERSITY,

Plaintiffs-Appellants,

v.

TRANSKARYOTIC THERAPIES, INC.,

Defendant-Appellee.

DECIDED: October 9, 2003

Before RADER, SCHALL, and LINN, Circuit Judges.

Opinion for the court filed by Circuit Judge RADER. Opinion concurring-in-part and dissenting-in-part filed by Circuit Judge LINN.

RADER, Circuit Judge.

The United States District Court for the District of Delaware determined on summary judgment that Transkaryotic Therapies, Inc. (TKT) did not infringe Genzyme Corporation's and Mount Sinai School of Medicine's (collectively, Genzyme) patent on methods of producing the human enzyme a–galactosidase A. Because Genzyme cannot prove infringement of the properly construed claims, this court affirms.

I.

Genzyme Corporation is the exclusive licensee of U.S. Patent No. 5,356,804 (the '804 patent), issued October 18, 1994, and assigned on its face to Mount Sinai School of Medicine of New York University. The '804 patent claims a method of producing human a–galactosidase A (a-Gal A) and cells engineered to express and secrete active human a–Gal-A. Administration of the a–Gal A protein treats patients suffering from Fabry disease, a condition triggered by a deficiency in this enzyme.

The claims at issue in this appeal are independent claims 1 and 10 of the '804 patent, which read as follows (emphases added):

1. A method for producing human a–galactosidase A comprising:
   (a) culturing a mammalian cell containing a chromosomally integrated nucleotide sequence encoding human a–galactosidase A controlled by a regulatory sequence that promotes gene expression and a selectable marker controlled by the same or different regulatory sequence, so that the a–galactosidase A nucleotide sequence is stably overexpressed and an enzymatically active a–galactosidase A enzyme is secreted by the mammalian cell; and
   (b) isolating enzymatically active a–galactosidase A enzyme from the mammalian cell culture.

10. A mammalian cell comprising a chromosomally integrated nucleotide sequence encoding human a–galactosidase A controlled by a regulatory sequence that promotes gene expression and a selectable marker controlled by the same or different regulatory sequence, so that the a–galactosidase A nucleotide sequence is stably overexpressed and an enzymatically active a–galactosidase A enzyme is secreted by the mammalian cell.

Genzyme filed suit against TKT, alleging infringement of the '804 patent. TKT's allegedly infringing product involves a technique known as gene activation. Under this technique, a DNA sequence acting as a promoter is inserted into a human host cell, whereupon the endogenous human cellular gene encoding α-Gal A is activated to express the endogenous human α-Gal A protein. It is undisputed that TKT's technique does not introduce an exogenous α-Gal A gene into human host cells.

The district court construed independent claims 1 and 10 of the '804 patent in a Markman hearing. See Markman v. Westview Instruments, Inc., 52 F.3d 967 (Fed. Cir. 1995)(en banc), aff'd, 517 U.S. 370 (1996). The trial court specifically addressed four disputed claim terms. Of these disputed terms, the most important is "chromosomally integrated," which the district court defined to mean "the combining or bringing together or merging of separate elements,"

specifically the "chromosome of a host cell" and "an exogenous nucleotide sequence encoding human a–galactosidase A with a promoter and selectable marker." Genzyme Corp. v. Transkaryotic Therapies, Inc., No. 00-677-GMS, 2001 WL 1530375, at *1 (D. Del. Nov. 28, 2001)

Following the Markman proceedings, both Genzyme and TKT moved for summary judgment on infringement. In its summary judgment motion for noninfringement, TKT explained that it produces human a–Gal A from cells genetically engineered to overproduce this enzyme via gene activation. TKT's gene activation process permits controlled expression of endogenous human a–Gal A in target cells. TKT argued it does not practice the claimed method because the "chromosomally integrated" limitation requires exogenously introduced gene sequences, a step the gene activation protocol does not utilize.

A week after filing its motion for summary judgment of infringement, Genzyme asked the district court to clarify its interpretation of the claim term "chromosomally integrated," particularly with respect to the meaning of the phrase "exogenous nucleotide." The district court complied with Genzyme's request, stating that the term "exogenous" referred to nucleotide sequences "exogenous to the host cell, not exogenous to the chromosomal site." Based on this meaning of the term "chromosomally integrated," Genzyme conceded it could not prevail on infringement. Thereafter, the district court issued an order granting TKT's summary judgment motion.

Genzyme timely appealed the district court's decision, arguing that the district court erred in defining the claim terms "chromosomally integrated," "regulatory sequence," "stably," and "comprising." This court has exclusive jurisdiction to hear Genzyme's appeal. 28 U.S.C. § 1295(a)(1) (2000).

II.

Claim construction is a matter of law, which this court reviews without deference. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). This court also reviews grants of summary judgment without deference. Johns Hopkins Univ. v. Cellpro, Inc., 152 F.3d 1342, 1353 (Fed. Cir. 1998).

"Chromosomally Integrated"

The dispute in this case turns on the meaning of "chromosomally integrated." Essentially, does the term "chromosomally integrated" require the action of inserting a human α-Gal A gene into the host chromosome, as argued by TKT, or can it cover a gene activation technique in which only a promoter sequence is inserted into a human host cell in order to activate the α-Gal A gene already present in the host cell, as argued by Genzyme.

The district court construed "chromosomally integrated" to mean "the combining or bringing together or merging of separate elements." Further the district court reasoned: "In this case, the separate elements that are combined are the chromosome of the host cell and an **exogenous** nucleotide sequence encoding human

a–galactosidase A with a promoter and selectable marker." Genzyme, 2001 WL 1530375, at *1 (emphasis added). Genzyme argues that the claims do not specify the origin of nucleotide sequences to be inserted into a target cell's chromosome. According to Genzyme, the term "chromosomally integrated" requires only that "a chromosome in the cell must contain a nucleotide sequence that encodes human a–Gal A enzyme." In other words, Genzyme argues, this claim term "requires the a–Gal A coding sequence to be located in a chromosome," regardless of whether the coding sequence originated within the cell or outside the cell. Thus, Genzyme asserts that the district court impermissibly limited the claim to the preferred embodiment of integrating an a–Gal A coding sequence into a host cell from an exogenous source.

The patent does not expressly define "chromosomally integrated." Rather, this court, like the district court, must derive the meaning of the term from its usage and context. A fundamental principle for discerning a term's usage is the ordinary and accustomed meaning of the words amongst artisans of ordinary skill in the relevant art at the time of invention. See Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1342 (Fed. Cir. 2001). Indeed, normal rules of usage suggest a "heavy presumption" that claim terms carry their accustomed meaning in the relevant community at the relevant time. CCS Fitness, Inc. v. Brunswick Corp., 288 F.3d 1359, 1366 (Fed. Cir. 2002) (citing Johnson Worldwide Assocs. Inc. v. Zebco Corp., 175 F.3d 985, 989 (Fed. Cir. 1999)). Of course, patent law has acknowledged that a patent applicant

may overcome this presumption by clearly using the words in the specification, prosecution history, or both "in a manner inconsistent with its ordinary meaning." Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1347 (Fed. Cir. 2003) (citing Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1325-26 (Fed. Cir. 2002)). In other words, a patent applicant may consistently and clearly use a term in a manner either more or less expansive than its general usage in the relevant community, and thus expand or limit the scope of the term in the context of the patent claims. Ballard Med. Prods. v. Allegiance Healthcare Corp., 268 F.3d 1362, 1361 (Fed. Cir. 2001) (noting that an applicant may disclaim claim scope during prosecution); Middleton, Inc. v. Minn. Mining & Mfg. Co., 311 F.3d 1384, 1388 (Fed. Cir. 2002) (explaining that in order to disavow claim scope, a patent applicant must clearly and unambiguously express surrender of subject matter during prosecution). In ascertaining the accustomed usage of the relevant community at the relevant time, dictionaries and treatises may serve to inform the courts. Tex. Digital Sys., Inc. v. Telegenix, Inc., 308 F.3d 1193, 1202-03 (Fed. Cir. 2002).

Standing alone, the words "chromosomally integrated" suggest uniting two separate portions of genetic material to form a more complete or purposeful whole. To one skilled in the art of molecular biology, "integration" generally means "insertion [of a DNA sequence] into a host genome as a region covalently linked on either side to the host sequences." Benjamin Lewin, Genes IV 812 (1990). Thus, the claim language suggests incorporation of exogenous genetic code into the chromosomal material of the host cell. In context, the asserted claims explain that the exogenous sequence has a regulatory sequence that causes the host cell to stably overexpress a–Gal A. The cell then secretes the excess a–Gal A. Again the word "integrated" suggests putting exogenous nucleotide sequences into the host cell's chromosome to facilitate this process. This word, however, does not conclusively evince whether one of skill in the art at the time of the invention would understand the exogenous sequences to come from outside the host cell, i.e., a vector, or from within the host cell but outside the critical chromosome, i.e., a transposable element. In this regard, perhaps the best tool to put the claims in proper temporal and technical context is the patent specification itself.

Throughout the ’804 patent specification, the applicant consistently uses the term “integrated” to refer to a foreign gene inserted into a host cell chromosome. See, e.g., ’804 patent at col. 14, ll. 14-19 (stable integration of plasmid DNA into host cell chromosomes); col. 24, ll. 42-46 (transfection of human sequences into African green monkey kidney (COS) cells); col. 24, ll. 60-64 (transfection of human sequences into Chinese Hamster Ovary (CHO) cells); col. 25, ll. 1-2 (amplification of integrated plasmid DNA in CHO cells); and col. 26, ll. 59-66 (transcription of stably integrated vector DNA in CHO cells). Indeed, the multitude of working examples, drawings, and diagrams of the ’804 patent show the insertion of foreign a–Gal-A coding sequences into host cells to generate excessive expression of the protein.

Notably, the “Summary of the Invention” explicitly states that the “present invention,” not merely a preferred embodiment, “involves the production of large quantities of human a–Gal A by cloning and expressing the a–Gal A coding sequence in eukaryotic host cell expression systems.” ’804 patent, col. 6, ll. 22-30. Likewise, the abstract of the ’804 patent describes recovery in “good yield” of “recombinant a–Gal A” from “engineered host cells.” The patent thus specifically uses “host cells” to express large quantities of a–Gal A. The term “host cell” means that the cell “hosts” or “receives” genetic material other than its own to perform its service. See Lewin, supra at 41 (explaining that viruses lack a cellular structure of their own, and must infect a “host cell” to effect replication); see also Bernard R. Glick and Jack J. Pasternak, Biotechnology 717 (2003) (defining a “host” to be “[a] microorganism, organism, or cell that maintains a cloning vector); Chambers Dictionary of Science and Technology 570 (Peter M.B. Walker, ed., 1999) (defining a “host” as meaning “in molecular biology that in which a plasmid or virus can replicate”). Thus, the invention involves “cloning and expressing the a–Gal A coding sequence in eukaryotic host cell expression systems,” an explanation one of skill in the art would read as introducing exogenous cloned sequences into a host cell for expression. This definition of the invention does not embrace targeting or activation of an endogenous gene.

In reading the specification to teach that “chromosomally integrated” means introducing genetic material exogenous to a host cell, not just a chromosome, this court is aware that

various portions of the patent vaguely refer to using less than the full endogenous coding sequence for expressing a–Gal A. In section 5.1, entitled "The a–Gal A CODING SEQUENCE," the patent recites:

> Although portions of the coding sequences may be utilized, full length clones, i.e., those containing the entire coding region for a–Gal A, may be preferable for expression.

'804 patent, col. 10, ll. 61-63; see also, col. 10, ll. 51-52. In the first place, this passage does not expressly refer to activation of endogenous genes at all. Rather in context, this passage merely explains that less than the entire coding sequence may be used to express a functional a–Gal A protein.

Indeed, this passage in context explains that this potential abbreviated coding sequence would come from outside the host cell. Specifically, the patent proceeds to explain in section 5.2 that "[i]n order to express a biologically active a–Gal A, the coding sequence for the enzyme, a functional equivalent, or a modified sequence, as described in Section 5.1., supra, is inserted into an appropriate eukaryotic expression vector, i.e. a vector which contains the necessary elements for transcription and translation of the inserted coding sequence in appropriate eukaryotic host cells." '804 patent at col. 12, ll. 35-42 (emphasis added). Once again, the specification emphasizes introduction of exogenous genetic material into host cells.

Similarly, one sentence fragment taken out of context in column 14, lines 10-14, mentions transforming a host cell with a controllable DNA, rather than the entire a–Gal A sequence: "[H]ost cells can be transformed with the a–Gal A or DNA controlled by appropriate expression control elements (e.g. promoter…), and a selectable marker." This reference, however, falls under the heading "Construction of Expression Vectors and Preparation of Transfectants." This entire section refers to creating a vector for "expression of a–Gal A in the [chosen] host cell." '804 patent, col. 13, ll. 11-13; see also, col. 12, ll. 55-58. Indeed the sentence preceding the fragment out of context refers expressly to the "introduction of foreign DNA," not targeting of endogenous DNA:

For long-term, high yield production of recombinant proteins, stable expression is

> preferred. For example, **following introduction of foreign DNA**, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then switched to a selective media. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with the a–Gal A or DNA controlled by appropriate expression control elements (e.g. promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. (Emphasis added.)

'804 patent, col. 14, ll. 4-19. The underlined sentence fragment from column 14, when read in context, does not suggest that gene targeting of endogenous coding sequences is possible within a host cell. Rather, the passage states host cells may be "transformed with the a–Gal A" (i.e. the gene in its entirety) or with "DNA controlled by appropriate expression control elements and a selectable marker." As noted in bold type above, the DNA in column 14 is foreign DNA introduced into host cells via vectors. The passage teaches that expression vectors containing viral origins of replication are not used to facilitate stable expression of a–Gal A. Instead, column 14 teaches the use of recombinant plasmids containing other expression control elements, such as promoters and enhancers, to continuously drive the expression of the a–Gal A DNA located in the plasmids for "long-term, high-yield production of recombinant proteins." '804 patent at col. 14, ll. 4-19.

Therefore, the sentence fragment in column 14, when read in context, teaches the introduction into host cells of exogenous DNA encoding a–Gal A, together with promoters and enhancers in recombinant plasmids. This passage does not suggest the introduction into a cell of expression control elements and a portion of a coding sequence to drive the expression of genes endogenously located within the host cell. Thus, the isolated passages in columns 10 and 14 do not even remotely suggest that "chromosomally integrated" means targeting of sequences encoding a–Gal A that are endogenous to a host cell.

Even if, arguendo, the cited passages did teach an example of gene targeting, such gene targeting would still require the introduction of exogenous nucleotide sequences encoding human a–Gal A. Gene targeting typically involves the transfection of a vector

containing a gene sequence into a cell containing an endogenous form of the gene. Upon transfection, the exogenous vector targets the endogenous gene, homologous recombination occurs, and exogenous sequences become part of the genome.[1] This process requires the introduction of at least some foreign gene DNA into the host cell, and is not the same as transposable elements rearranging genes within a cell. No record evidence suggests that the specification contemplates, much less defines, the integration and expression of genes outside a chosen chromosome, but within a cell via transposable elements.

The prosecution history, like the specification, does not permit a broad interpretation of the claim term "chromosomally integrated." The original claims of the '804 patent recited a method of producing human a–Gal A protein and cells for producing this enzyme transformed with a recombinant vector encoding a–Gal A. The examiner rejected these claims under 35 U.S.C. § 112(1) for lack of enablement because the applicant had not deposited the claimed vector. The examiner considered the deposit "essential" to the claimed invention. The applicant conceded, and made the deposit without arguing against the requirement. Thus, during prosecution, the applicant agreed that the pending claims required a recombinant vector encoding a–Gal A. Later, the applicant amended the claims to remove the term "recombinant vector," but neither the examiner nor the applicant suggested that the amendment rendered the deposit unnecessary. Thus, the prosecution history shows the necessity of the deposited exogenous vector sequences to the '804 patent claims.

During prosecution, the applicant also made arguments to overcome prior art that are inconsistent with a broad interpretation of the claim term "chromosomally integrated." The examiner rejected the claims under 35 U.S.C. § § 102 and 103 in view of prior art that allegedly taught the assembly of expression vectors containing human a–Gal A sequences. Specifically, the examiner rejected the pending claims over "the genomic clone containing the promoter for the human a–Gal A gene disclosed by Quinn, or the a–GalA cDNAs disclosed by Tsuji, Bishop, Coppola or Calhoun." Based on this prior art, according to the examiner, "it would have been obvious to assemble other expression vectors containing full length a–GalA gene sequences."

The applicant responded by distinguishing the prior art. In particular, the applicant noted that the prior art references achieved only low level, transient, expression of human a–Gal A when full-length cDNA sequences were introduced into COS cells. According to the applicant, transient expression systems of Tsuji and Bishop "could not be utilized to produce a–Gal A, since recombinant protein could not be recovered from the system." The applicant further stated: "In contrast to the prior art failures, and to the Applicants' surprise, the human a–GalA gene product, when stably expressed in mammalian cell systems, is not only expressed at remarkably high levels, but is actually selectively secreted at very high levels out of the host cell so that facile recovery of the active product is finally made possible." The applicant then stressed that recovery of active a–Gal A was an element of the pending method claims.[2]

These arguments did not persuade the examiner, who again issued the same rejections. The examiner noted: "The selection of the appropriate plasmids, promoters, selectable markers and cell lines for proper expression of the inserted gene is merely a matter of judicious selection, within the scope of the ability of one ordinarily skilled in the art." Without further recourse, the applicant submitted an amendment after final rejection under 37 C.F.R. § 1.116. This amendment to clarify the points of disagreement with the examiner also included a declaration by Dr. Ira Mellman. In his declaration, Dr. Mellman asserted his surprise at the inventive expression scheme disclosed in the denied claims, noting the difficulty of purifying heterologously expressed recombinant proteins. By definition, a heterologously expressed recombinant protein is not naturally or normally expressed by a particular tissue or cell type. A "heterologoous protein" is recognized by those of skill in the art as being a recombinant protein "whose amino acid sequence is encoded by a cloned gene." Glick, supra at 717, 725; see also J.M. Lackie and J.A. T. Dow, The Dictionary of Cell and Molecular Biology, 212 (1999) (defining heterologous to mean "[d]erived from the tissues or DNA of a different species"); Encyclopedia of Microbiology, 1012 (Joshua Lederberg, ed., 2000) (defining "heterologous" to mean "derived from a different source or species; not native to the host"). Dr. Mellman did not suggest that the claimed expression method embraced expression of endogenous genes.

Moreover, in its clarifying amendment, the applicant stressed again that the prior art did

not teach the "stable expression of human a–galactosidase A and isolation of enzymatically active a–galactosidase A from an engineered mammalian cell system." Eukaryotic host expression systems, such as the systems delineated in section 5.2.1 of the '804 patent, have long been understood by those of skill in the art as expression vector systems that facilitate expression of eukaryotic genes. See James D. Watson, et al., Molecular Biology of the Gene, 614, 615 (1987) ("The more we learn about how gene expression is controlled in eucaryotes, the more intelligently we can develop expression vector systems … . Several factors already encourage the development of eucaryotic systems for the expression of eucaryotic genes."); Susan Bright, et al., From Laboratory to Clinic: The Development of an Immunological Reagent, 112 Immunology Today 130-31 (1991) (discussing "eukaryotic expression systems," including CHO cells transfected with an expression plasmid for the production of recombinant antibodies); Glick, supra, at 181-87 (describing "mammalian cell expression systems" as being composed of cell lines, such as COS and CHO cells, engineered with mammalian expression vectors to express heterologous proteins). In other words, the applicant expressly confined the invention to production of proteins by introducing vectors into a mammalian host cell.

The examiner persisted in the rejection until the applicant submitted a supplemental amendment under 37 C.F.R. § 1.116. The amendment replaced the phrase "transformed with a recombinant vector which includes a nucleotide sequence encoding a–galactosidase A" with the phrase "chromosomally integrated nucleotide sequence encoding human a–galactosidase A." The examiner and applicant agreed on this language during an after-final rejection examiner interview. The record does not explain the reasons the examiner finally accepted this language.

Contrary to Genzyme's position, this eleventh-hour amendment did not operate to broaden the claims to eliminate the requirement of insertion of an exogenous gene into a host cell. In the first place, the deposit requirement, the specification, the applicant's arguments to distinguish prior art, the examiner's responses, and Dr. Mellman's declaration repeatedly stressed that the invention envisioned insertion of an exogenous gene sequence into a host

cell. A clarifying amendment at the last moment could not negate that extensive public record.

More important, the examiner could not accept a second (supplemental) after-final amendment broadening the scope of the rejected claims without formal comment from the applicant. Under the applicable Patent Office rules, amendments to patent claims after final rejection cannot alter the substantive scope of the claims without explanation about the necessity of the amendment and without reasons for the delay in proposing the change.[3] See 37 C.F.R. § 1.116(b) (1992) ("If amendments touching the merits of the application . . . are presented after final rejection . . . they may be admitted upon showing of good and sufficient reasons why they are necessary and were not earlier presented."). If this amendment markedly broadened the claims, it satisfied neither of those requirements. The record supplies no explanation from the applicant or the examiner that these changes were both "necessary" and justifiably "not earlier presented." Thus, according to PTO rules, the examiner could not have allowed this amendment if it changed at all the scope of the claims set forth in the deposit requirement, the specification, the arguments of the applicant, and Dr. Mellman's declaration.

The record instead suggests that the examiner felt this last-minute change did not alter the scope of the claims. The examiner's comments did not distinguish these newly amended claims from the prior art, but simply noted that the claims had to recite that the a–Gal A was overexpressed and secreted. Likewise, the applicant did not address any change in the scope of the claims. In any event, the examiner could not have permitted any Rule 116 amendment that expanded the claims to make the introduction of exogenous DNA into a host cell optional.

Thus, the prosecution history indicates that the term "chromosomally integrated" requires introduction of exogenous a–Gal A sequences into the host cell. The claims of the '804 patent recited these exogenously introduced a–Gal A sequences until after prosecution on the merits was closed. The record simply does not show that the examiner, contrary to PTO rules, vastly broadened these claims upon entering the supplemental after final amendment to embrace overexpression of human a–Gal A sequences endogenous to a host cell. The informed public

could only understand this prosecution history, as well as the specification and the claim language itself, to limit Genzyme as reflected throughout the prosecution.

TKT argues that if this court reads the claims as suggested by Genzyme, they would be invalid. Indeed this court notes that the '804 specification and figures do not discuss any methods of activating endogenous a–Gal A gene sequences. In fact, the specification does not discuss "chromosomally integrated" sequences as endogenous a–Gal A genes within the host cells at all. Thus, the record would appear to raise questions of enablement. See Modine Mfg. Co. v. United States Int'l Trade Comm'n, 75 F.3d 1545, 1557 (Fed. Cir. 1996) (this court interprets claims "so as to preserve their validity" whenever "reasonably possible"). The district court, however, did not decide validity issues, and this court need not examine enablement to properly define the claim term "chromosomally integrated" in view of the specification and prosecution history.

This court also notes that this case is different from Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003), which accorded a broad reading to similar claims. This court in Amgen did not confront a prosecution history and specification that conclusively limits the scope of the disputed claim terms. In this case, both the specification and the prosecution history indicate that the patentee employed the term "chromosomally integrated" in a manner inconsistent with a broad textbook meaning that envelopes both endogenous and exogenous sources of sequences encoding genes in a host cell. See Bruce Alberts, et al., Molecular Biology of the Cell, 247-50 (1983) (discussing integration of transposable elements into the genomes of cells); Lewin, supra at 697-702 (discussing the introduction and integration of exogenous donor DNA into recipient cells in generating stably expressing host cell lines and transgenic animals). Therefore, the district court did not err in construing this claim term to require the introduction into a host cell of exogenous sequences encoding a–Gal A.

"Regulatory Sequence"

The district court construed "regulatory sequence" in the first occurrence to mean "any

and all sequences required for gene expression of the human a–galactosidase A gene, consisting of at least one sequence which promotes gene expression." Column 14, ll. 9-14, of the '804 patent discloses several examples of regulatory sequences that are appropriate expression control elements. While the specification teaches a process requiring one or more of these elements to transform cells with a–Gal A DNA, it does not teach that all of them are required. The district court erred in this regard, but the error is harmless in view of the trial court's proper construction of the claim term "chromosomally integrated."

"Stably"

The district court construed the claim term "stably" in the phrase "stably overexpressed" to require that "the nucleotide sequence encoding human a–galactosidase A stays in place once integrated into the chromosome, i.e. the chromosomal change is not transient." During prosecution, the examiner rejected the claims for indefiniteness under §112(2). In response, the applicant gave the examiner a definition of "stably," namely a "stable level and duration of expression of the human a–galactosidase A gene." This definition, as the applicant noted, "denotes persistent expression, as distinguished from the short-term transient expression systems of the prior art."

Indeed the specification discloses several working examples that show the stable expression of the human a–galactosidase A gene. The specification particularly points out that the applicant disclosed high levels of a–Gal A expression can be achieved with vectors that do not integrate into the host's chromosome. Instead, these vectors achieve stable extra-chromosomal expression via transcription of cDNA in the presence of a selectable marker. See '804 patent at col. 13, ll. 63-67. Thus, the invention as described in the specification achieves stable expression by chromosomal integration and extra-chromosomal gene expression. The applicant surrendered the extra-chromosomal embodiment of stable expression during prosecution.

Thus, the district court correctly discerned that the claims only embrace stable expression of gene sequences integrated into a host's chromosome. However, the

specification and prosecution history do not discuss this stability in terms of duration of chromosomal change. Rather, the applicant explicitly described the term "stably" as referring to the level and duration of gene expression. Therefore, the district court erred in construing this term, but the error is harmless given the proper construction of the claim term "chromosomally integrated."

III.

After construing the claims of the '804 patent, the district court granted summary judgment of noninfringement to TKT. Summary judgment is appropriate "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c); Celotex Corp. v. Catrett, 477 U.S. 317, 322 (1986). In deciding whether a genuine issue of material fact exists, this court draws all justifiable inferences in the nonmovant's favor. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 255 (1986).

As noted above, the TKT method of overexpression involves gene activation. Under this method, TKT inserts promoters into human host cells that "switch on" the endogenous human cellular gene encoding a–Gal A. TKT's protocol does not introduce exogenous genes into host cells. Genzyme hinged its claim of infringement on a claim interpretation broad enough to encompass gene targeting. TKT provided declaratory evidence showing that the '804 patent did not teach one of skill in the art a workable method of introducing an exogenous gene sequence into a cell to recombine with an endogenous gene residing in the host chromosome (gene targeting) to facilitate gene activation. The district court did not decide this validity issue, but instead, after construing the claims, credited TKT's declaratory evidence that its gene activation method does not infringe Genzyme's process. Genzyme concedes it cannot show infringement by TKT if the '804 patent claims require the introduction into a host cell of exogenous sequences encoding a–Gal A. Because the claims require this exogenous sequence element, Genzyme's concession precludes a finding that TKT infringes the asserted claims of the '804 patent. Therefore, the district court properly granted summary judgment of

noninfringement to TKT.

CONCLUSION

The district court properly construed the claim term "chromosomally integrated," but erred in construing the disputed terms "regulatory sequence" and "stably." However, because the construction of the claim term "chromosomally integrated" precludes Genzyme from showing infringement, these latter errors are harmless. Therefore, this court affirms the district court's grant of summary judgment.

COSTS

Each party shall bear its own costs.

AFFIRMED

United States Court of Appeals for the Federal Circuit

02-1312

GENZYME CORPORATION

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TRANSKARYOTIC THERAPIES, INC.,

Defendant-Appellee.

LINN, Circuit Judge, concurring-in-part and dissenting-in-part.

While I concur in the majority's construction of the claim limitations "regulatory sequence" and "stably overexpressed," I must respectfully dissent from its conclusion regarding the construction of the "chromosomally integrated" limitation. In my view, the restriction of the scope of this limitation to require the introduction into a host cell of "exogenous sequences encoding ?-Gal A," Genzyme, slip op. at 18, unadvisedly reads limitations from the specification into the claims. I can discern no proper basis to do so and would give the "chromosomally integrated" limitation the full scope of its ordinary and customary meaning.

I. CLAIM CONSTRUCTION

A. Ordinary and Customary Meaning

It is well settled in our jurisprudence that claim terms are to be given their ordinary and customary meaning to one of skill in the relevant art. Johnson Worldwide Assocs., Inc. v. Zebco Corp., 175 F.3d 985, 989 (Fed. Cir. 1999). Determining the ordinary and customary meaning of the terms of the claims is the first step in claim construction, and consultation of the written description and prosecution history before attempting to ascertain the ordinary and customary meaning of the language of the claims is premature. Tex. Digital Sys., Inc. v. Telegenix, Inc., 308 F.3d 1193, 1204 (Fed. Cir. 2002). Where the patentee's choice of a claim term "deprive[s] the claim of clarity,'" CCS Fitness, Inc. v. Brunswick Corp., 288 F.3d 1359, 1367 (Fed. Cir. 2002), however, the court must "resort to the other intrinsic evidence," id., to determine the meaning of the claim terms.

In my view, the majority hastens too quickly past the fundamental step of determining the ordinary and customary meaning of "chromosomally integrated." It relies on a single definition of "integration," defined in the context of "viral or another DNA sequence," to import the concept of a "host genome." Genzyme, slip op. at 6; Benjamin Lewin, Genes IV 812 (1990). In light of this imported concept of a "host cell," the majority perceives ambiguity as to "whether one of skill in the art at the time of the invention would understand the exogenous sequences to come from outside the host cell, i.e., a vector, or from within the host cell but outside the critical chromosome, i.e., a transposable element."[4] Genzyme, slip op. at 6. It then turns to the specification to resolve this perceived ambiguity.

With all due respect to my colleagues, there is no ambiguity here to be resolved. The majority opinion establishes that the term "chromosomally integrated" could be used in reference to the incorporation into a chromosome of either endogenous or exogenous DNA, that is to say, DNA sequences that have their origin either inside or outside the cell to which the chromosome is native. The ordinary and customary meaning of the term broadly encompasses both possibilities. It is incorrect to perceive a claim term as ambiguous merely because of its breadth and to require that the term be redefined to encompass only a portion of its ordinary meaning in the name of clarity.

Technical treatises publicly available at the time a patent is issued may be consulted as "reliable sources of information that would have been attributed to the terms of the claims by those of skill in the art." Tex. Digital Sys., 308 F.3d at 1202-03. See also Inverness Med. Switz. GmbH v. Princeton Biomeditech Corp., 309 F.3d 1365, 1370 (Fed. Cir. 2002) ("We may look, therefore, to the dictionary definition of the claim term 'mobility' as of the date the patents issued."). A review of the relevant technical treatises contemporaneous with the issuance of the '804 patent shows that "chromosomally integrated" had a broad meaning, encompassing the integration of both exogenous and endogenous DNA. The Genes IV text that the majority cites uses the term "integrated" to describe both the incorporation of viral DNA of extracellular origin, Genes IV 674 (1990) ("One or more [viral] DNA copies become integrated into the host genome."), and the transposition of yeast transposable elements from one site to another within the same genome, id. at 681 (describing yeast Ty transposable elements as subject to "reverse transcription and integration"). Transposable elements, such as retroposons, were understood at the time to be a part of an organism's own genome. Id. at 672 ("[W]e think of retroposons as genomic (duplex DNA) sequences that occasionally transpose within a genome; they do not migrate between cells."). Another contemporaneous leading text similarly describes both viral DNA and transposable element DNA as integrating into the chromosome.

Bruce Alberts et al., Molecular Biology of the Cell 255 (1989) ("[T]he DNA circle [of the transposable element] integrates into a randomly selected site on the chromosome.") The term "chromosomally integrated" was thus commonly understood by those of skill in the art at the time to refer to the incorporation into a chromosome of DNA that either came from another site in the same genome or from outside the cell. This is the ordinary and customary meaning of the claim term.

B. The Intrinsic Record

The next step in the claim construction process in this case, as in every case, is to examine the intrinsic evidence, comprising the claims, the written description, and the prosecution history if in evidence, to determine whether the patentee has rebutted the presumption that "chromosomally integrated" has its ordinary and customary meaning. See Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc., 334 F.3d 1294, 1298 (Fed. Cir. 2003); Tex. Digital Sys., 308 F.3d at 1204. A patentee may rebut this presumption by "defin[ing] claim terminology in a manner inconsistent with its ordinary meaning," Biovail Corp. Int'l v. Andrx Pharms., Inc., 239 F.3d 1297, 1301 (Fed. Cir. 2001), or by disclaiming a particular interpretation of a claim term during prosecution, Biodex Corp. v. Loredan Biomedical, Inc., 946 F.2d 850, 863 (Fed. Cir. 1991). I find no redefinition of the claim term in the intrinsic evidence, nor do I discern any disclaimer of coverage of the integration of endogenous DNA.

The word "integrated" or "integration" appears nine times in the sixty-page '804 written description. None of these instances on its own amounts to a "special definition . . . clearly stated in the patent specification." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996). The majority correctly notes that "the applicant consistently uses the term 'integrated' to refer to a foreign gene inserted into a host cell chromosome." Genzyme, slip op. at 7. However, this use of "integrated" is not "inconsistent with [its] ordinary meaning," Vitronics Corp., 90 F.3d at 1582, and cannot therefore be used to show that the patentee has redefined the term "with reasonable clarity, deliberateness, and precision," In re Paulsen, 30 F.3d 1475, 1480 (Fed. Cir. 1994). As the majority demonstrates, the ordinary and customary meaning of "integrated" embraces the incorporation of both exogenous and endogenous DNA. It is immaterial to the proper construction of "integrated" that the embodiments consistently employ exogenous DNA. Absent a redefinition or disclaimer relating to a claim term, consistent use in the written description of a term in a narrower meaning cannot trump a broader ordinary and customary meaning of the term as used in a claim. Were it otherwise, the scope of claim terms would regularly be limited to the embodiments disclosed in the specification. But it is the claim language, not the embodiments, which control. See Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1248 (Fed. Cir. 1998) ("[T]he claims define the scope of the right to exclude; the claim construction inquiry, therefore, begins and ends in all cases with the actual words of the claim.").

The majority also cites the "Summary of the Invention" section, where "the present invention" is said to involve "host cell expression systems," and the abstract, which refers to "engineered host cells." '804 patent, col. 6, ll. 22-25; Abstract. The majority contends that the term "host cell" necessarily implies the introduction of exogenous genetic material, and this amounts to a "definition of the invention." Genzyme, slip op. at 8. In other words, the majority sees a redefinition of the claim term "chromosomally integrated" in the use in the specification of a term, "host cell," that appears nowhere in the claims. In my view, the majority roams too far afield in search of a redefinition of the claim term. It is clear from our precedent that any redefinition must focus on the term actually employed in the claims. See Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1324 (Fed. Cir. 2002) ("The claim language defines the bounds of claim scope."); Interactive Gift Express, Inc. v. Compuserve Inc., 256 F.3d 1323, 1331 (Fed. Cir. 2001) ("In construing claims, the analytical focus must begin and remain

centered on the language of the claims themselves, for it is that language that the patentee chose to use to 'particularly point[ ] out and distinctly claim[ ] the subject matter which the patentee regards as his invention.'"); Thermalloy, Inc. v. Aavid Eng'g, Inc., 121 F.3d 691, 693 (Fed. Cir. 1997) ("[T]hroughout the interpretation process, the focus remains on the meaning of claim language.").

Like the written description, nothing in the prosecution history limits or redefines the scope or meaning of "chromosomally integrated." The majority stresses the fact that "during prosecution, the applicant agreed that the pending claims required a recombinant vector encoding ?-Gal A." Genzyme, slip op. at 11. However, this was predicated on the fact that the set of claims then pending explicitly required the use of a recombinant vector. The Examiner made clear that a deposit of the vector was required because the vector was present in the claims:

> Since the vector(s) is/are essential to the claimed invention it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the vector(s) is/are not so obtainable or available, the requirements of 35 USC 112 may be satisfied by deposit(s) of the vector(s).

As the majority notes, the claims were later amended to remove the term "recombinant vector," and the issued claims do not contain such a limitation.

Despite the removal of that limitation, however, the majority maintains that the deposited vector sequence remained necessary to the claimed invention, and this mandates a restriction of the scope of "chromosomally integrated." I cannot agree. The deposit of the recombinant vector was required by the Examiner to establish enablement of then-pending claims that explicitly required its use. When the use of a recombinant vector was eliminated from the claims, the predicate for the Examiner's deposition requirement evaporated. There is no reason to conclude in this case that an action taken as a result of the presence of a specific term in the claims should continue to bind the patentee when that term is removed during prosecution and does not appear in the issued claims. See Smith v. Snow, 294 U.S. 1, 16 (1935) ("It is of no moment that in the course of the proceedings in the Patent Office the rejection of narrow claims was followed by the allowance of the broader claim 1."); United States v. Telectronics, Inc., 857 F.2d 778, 783 (Fed. Cir. 1988) ("The arguments emphasizing the use of a skin electrode, which were made at the time the application claims explicitly

contained such a limitation, cannot furnish a basis for restricting issued claim 1, which lacks any such limitation."); Kistler Instrumente AG. v. United States, 628 F.2d 1303, 1308 (Ct. Cl. 1980) ("[D]efendant's insistance [sic] upon this court's reading back into the claims limitations which were originally there and were removed during prosecution of the application through the Patent Office cannot be permitted.").

The majority doubts, however, whether the removal of the "recombinant vector" limitation from the issued claims actually represented a broadening of the claims. Given that the amendment occurred at a late stage of prosecution, the majority states that if it were in fact broadening, the amendment would have been a violation of 37 C.F.R. § 1.116(b), because the patentee made no "showing of good and sufficient reasons why [it was] necessary and [was] not earlier presented." 37 C.F.R. § 1.116(b) (1992). A decision restricting the scope of an otherwise unambiguous claim term based on an applicant's presumed noncompliance with a procedural rule of the PTO strikes me as ill-founded. See Dethmers Mfg. Co., Inc. v. Automatic Equip. Mfg. Co., 293 F.3d 1364, 1366 (Fed. Cir. 2002) (Linn, J., dissenting from the order denying rehearing en banc) ("[O]nce a patent issues, non-compliance with a procedural rule administered by the PTO within the scope of the agency's statutory authority and found, by virtue of the grant of the patent, to have been satisfied during prosecution is, in and of itself, of no consequence.").

The majority also relies on arguments distinguishing certain prior art references to establish that the patentee "expressly confined the invention to production of proteins by introducing vectors into a mammalian host cell." Genzyme, slip op. at 14. To establish a disclaimer or disavowal of claim scope, of course, a patentee must use "words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." Tex. Digital Sys., 308 F.3d at 1204. The majority finds such a manifest exclusion of the use of a cell's own endogenous DNA in the patentee's assertions that the claimed invention was capable of recovering "recombinant protein," and that such "heterologously expressed recombinant proteins" are difficult to purify. Genzyme, slip op. at 12-13. The patentee also referred to the claimed invention's use of "an engineered mammalian cell system." Id., slip op.

at 14. I see no clear disavowal of the use of endogenous DNA in these remarks. Neither Tsuji nor Bishop employed endogenous DNA. The essence of the patentee's argument was that, while the prior art employed exogenous DNA to achieve a low level of transient expression, the claimed invention was "the first demonstration of the stable, overexpression, selective secretion, and subsequent isolation of a lysosomal enzyme in a recombinant mammalian cell system." Whether the prior art references integrated the cell's own DNA into a different chromosomal site was simply not at issue.

II. ENABLEMENT

The majority notes that "the record would appear to raise questions of enablement," although it also states that "this court need not examine enablement to properly define the claim term 'chromosomally integrated' in view of the specification and prosecution history." Genzyme, slip op. at 17. To the extent that enablement concerns underlie the majority's narrowing of the scope of "chromosomally integrated," however, I suggest that such issues are not yet ripe for consideration. The district court has not yet addressed validity, and the parties did not brief the issue on appeal. Although this court has stated that claims should be interpreted so as to preserve their validity whenever reasonably possible, Modine Mfg. Co. v. United States Int'l Trade Comm'n, 75 F.3d 1545, 1557 (Fed. Cir. 1996), it is wrong to allow enablement issues that have not yet been fully ventilated by the parties and the district court to influence a claim construction determination. I agree that all validity concerns should be left for another day.

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[1] Gene targeting is described in a 1987 Cell article (Kirk Thomas and Mario Capecchi, Site-Directed Mutageneis by Gene Targeting in Mouse Embryo-Derived Stem Cells, 51Cell 503-12 (1987)) and a 1985 Nature article (Oliver Smithies, et al., Insertion of DNA Sequences Into the Human Chromosomal b–globin Locus by Homologous Recombination, 317 Nature 230-34 (1985)), both of which are of record. The Thomas article notes: "Gene targeting-the homologous recombination of DNA sequences residing in the chromosome with newly introduced DNA sequences-provides a means for systematically altering the mammalian genome… . A desired alteration would first be introduced into a cloned DNA sequence, and gene targeting would then transfer the alteration into the genome." The Smithies article states:

"[t]he experiments reported here establish that the planned modification of a specific human gene can be accomplished in mammalian cells by homologous recombination without detectably affecting other parts of the genome."

[2] Secretion of enzymatically active a–galactosidase A is an element of all of the claims issued in the '804 patent, and isolation of this active enzyme is an element of all method claims of the '804 patent.

[3] The dissent contends that non-compliance with a Patent Office procedural rule is of no consequence once a patent issues. Dissent, slip. op. at 8. However, this court presumes that the Patent Office complies with its own rules, a presumption overcome only upon presentation of contrary evidence. Rite Hite Corp. v. Kelley Co., Inc., 819 F.2d 1120, 1123 (Fed. Cir. 1987) ("Kelley has provided neither evidence nor inference to overcome the presumption that the PTO complied with its own rules."). Therefore, without record support, an argument alleging dereliction of duty by a patent examiner is without merit.

[4] The majority's claim construction analysis frames the question as whether "chromosomally integrated" can be construed to "cover a gene activation technique in which only a promoter sequence is inserted into a human host cell in order to activate the ?-Gal A gene already present in the host cell," Genzyme, slip op. at 4, which is a description of TKT's allegedly infringing technique. I believe the question is misdirected. Our precedent informs that "claims [should] not be construed by reference to the accused device." NeoMagic Corp. v. Trident Microsys., Inc., 287 F.3d 1062, 1074 (Fed. Cir. 2002).