United States District Court,
D. Massachusetts.

GENENTECH, INC,
Plaintiff.
v.
BOEHRINGER MANNHEIM GmbH and Boehringer Mannheim Corp,
Defendants.

Civil Action No. 96-11090-PBS

Dec. 30, 1997.

Patentee brought action against competitor, alleging infringement of its patents relating to genetically engineered tissue pasminogen activator (t-PA). Following *Markman* hearing, the District Court, Saris, J., held that: (1) "organic synthesis" as used in patent meant production of oligonucleotide or fragment of a gene using organic chemistry without use of an enzyme; (2) "gene fragment" referred to either single or double-stranded deoxyribonucleic acid (DNA), of any length; (3) "tissue plasminogen activator" meant native human t-PA; (4) "pharmaceutical composition" meant compositions that were stable for appropriate periods of time, acceptable in their own right for administration to humans, and readily manufacturable; and (5) "molecular sieve" meant gel permeation or gel filtration techniques which separate molecules based on size.

Ordered accordingly.

4,432,832, 4,511,502, 5,034,225. Cited.

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MEMORANDUM AND ORDER

SARIS**, District Judge.**

INTRODUCTION

The plaintiff, Genentech, Inc. ("Genentech"), alleges that the defendants, Boehringer Mannheim GmbH and Boehringer Mannheim Corp. (collectively, "BM"), infringed five patents involving its tissue plasminogen activator ("t-PA") product. This memorandum and order addresses the issues of claims construction raised in a hearing held on June 17-18, 1997, and July 23, 1997, regarding three of Genentech's patents: United States Patent Nos. 4,432,832 ("the '832 patent"); 5,034,225 ("the '225 patent"); and 4,511,502 ("the '502 patent"). *See* Markman v. Westview Instruments, Inc., 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996).

The hearings consisted of extensive and impressive testimony by experts, including: Joseph Oliver Falkinham, III, professor of microbiology at Virginia Polytechnic Institute and State University; Andrew C. Webb, professor of biological sciences at Wellesley College; Victor Gurewich, M.D., director of the vascular research laboratory and co-director of the Institute for the Prevention of Cardiovascular Disease at Beth Israel-Deaconess Medical Center, and professor of medicine at Harvard Medical School; Jeffrey V. Ravetch, M.D., professor at the Rockefeller University and head of the laboratory of molecular genetics and immunology, and adjunct professorin the department of microbiology and immunology at Jefferson Medical College and Jefferson Cancer Institute; Alexander M. Klibanov, professor of chemistry at the Massachusetts Institute of Technology (M.I.T.); and Charles L. Cooney, a professor of chemical and biochemical engineering and executive officer of the department of chemical engineering at M.I.T. In addition, the Court heard testimony of an agreed-upon court-appointed neutral expert, Connie Cepko, a professor of genetics and associate investigator of the Howard Hughes Medical Institute at the Harvard Medical School.

The parties agreed at the Markman v. Westview Instruments, Inc., 52 F.3d 967 (1995) hearing on June 18, 1997 and on July 23, 1997, that the terms in dispute were: "organically synthesized" and "gene fragments" ('832 patent); "tissue plasminogen activator," "incorporating," and "pharmaceutical composition" (225 patent); and "molecular sieve" ('502 patent). (Tr. 2-117 -2-118.) FN1 At the urging of both parties, the hearings addressed only the claims construction issues and left pending the parties' cross-motions for summary judgment.

FN1. References to the Markman Hearing transcript will refer to the volume and the page. Thus, 2-117 refers to day two, page 117. The hearing on day one was June 1, 1997; day two was June 18, 1997 and day three was July 23, 1997.

I. FACTUAL BACKGROUND

Serious heart attacks can be caused by the presence of a thrombus, which is a blood clot in the coronary blood vessels or coronary artery. The process that dissolves a thrombus is called thrombolysis and the chemicals in the body that induce thrombolysis are called plasminogen activators. Two plasminogen activators, which are a natural part of a body's defenses, are urokinase-type plasminogen activator (u-PA or urokinase) and tissue-type plasminogen activator (t-PA).

T-PA is a chemical that makes the body's natural plasminogen become plasmin, an enzyme. Plasmin cuts through fibrin, the substance which makes up blood clots. Although the body naturally produces small amounts of t-PA, this quantity is insufficient to activate sufficient plasminogen to cut through the large clots involved in heart attacks.

In the late 1970s and early 1980s, scientists, whose research was sponsored by Genentech, successfully

reproduced t-PA through recombinant DNA technology by identifying the DNA encoding t-PA-527 amino acids with glycosylation (the attachment of sugars)-at three sites and inserting the DNA into bacteria. In July, 1979, Genentech applied for the '832 patent for its particular method of reproducing t-PA and subsequently obtained approval from the Food and Drug Administration (FDA) to sell t-PA under the brand name Activase. Genentech also obtained a patent for purifying proteins ('502 patent) in 1985 and one for increasing the solubility of t-PA in a pharmaceutical composition by incorporating arginine ('225 patent) in 1991.

Genentech claims that BM's plasminogen activator called Reteplase violates its patents.

II. THE PATENTS

A. '832 Patent

Entitled "Method of Constructing a Replicable Cloning Vehicle Having Quasi-Synthetic Genes," the '832 patent "provides a method of general applicability" for the production of useful proteins of known amino acid sequence, including antibodies and enzymes, and is "particularly suited to the expression of mammalian polypeptide hormones and other substances having medical applications." ('832 Patent, Col. 8, lines 3-11.) The inventors claim that their application represents "the first occasion upon which a medically significant human polypeptide was directly expressed microbially, rather than in conjunction with extraneous protein." ('832 prosecution history, Pl.Ex. 2, at p. 103.) To do this, the '832 patent teaches a method of making a plasmid using two types of DNA, synthetic DNA, and cDNA derived from messenger RNA. Id. (*See* '832 patent, Col. 10, lines 35 *et seq*.) Specifically, the '832 patent describes "a method of using organically-synthesized DNA to create an optimal 5' end (encoding the amino terminus of a protein) for the desired protein. The organically-synthesizedDNA is joined to the cDNA to create a chimeric [or semi-synthetic] gene." (Cepko report at 1, Docket 262.)

Claim 1 of the '832 patent teaches the method of constructing the "replicable cloning vehicle" capable of expressing a gene for a particular polypeptide of known amino acid sequence by combining cDNA and synthetic DNA. Steps (a) and (b) involve "obtaining by reverse transcription from messenger RNA gene fragments" which encode less than all of the amino acid sequence of the polypeptide. Step (c) involves providing by "organic synthesis one or more synthetic non-reverse transcript gene fragments" for the remainder of the sequence. Step (d) involves joining the gene fragment of Step (c) to the gene fragment described in Steps (a) and (b) and inserting these gene fragments into a plasmid in proper reading phase.

The disputed terms in Claim 1 are in bold type:

In the method of constructing a replicable cloning vehicle capable, in a microbial organism, of expressing a particular polypeptide of known amino acid sequence wherein a gene coding for the polypeptide is inserted into a cloning vehicle and placed under the control of an expression promoter, the improvement which comprises:

(a) obtaining by reverse transcription from messenger RNA a first gene fragment for an expression product other than said polypeptide, which fragment comprises at least a portion of the coding sequence for said polypeptide;

(b) where the first fragment comprises protein-encoding codons for amino acid sequences other than those contained in said polypeptide, eliminating the same while retaining at least a substantial portion of said

coding sequence, the resulting fragment nevertheless coding for an expression product other than said polypeptide;

the product of step (a) or, where required, step (b) being a fragment encoding less than all of the amino acid sequence of said polypeptide;

(c) providing by **organic synthesis** one or more synthetic non-reverse transcript-**gene fragments** encoding the remainder of the amino acid sequence of said polypeptide, at least one of said fragments coding for the amino-terminal portion of the polypeptide; and

(d) deploying the synthetic **gene fragment(s)** of step (c) and that produced in step (a) or (b), as the case may be, in a replicable cloning vehicle in proper reading phase relative to one another and under the control of an expression promoter;

whereby a replicable cloning vehicle capable of expressing the amino acid sequence of said polypeptide is formed.

B '225 Patent

The '225 patent, entitled "Stabilized Human Tissue Plasminogen Activator for Compositions," claims a method of increasing the solubility and stability of the protein human tissue plasminogen activator (t-PA) in a pharmaceutical composition by incorporating arginine. ('225 Patent, col. 9, 11. 32-35 -col. 10, 11. 24-25; Cepko report at 6.) Genentech alleges that BM infringes the '225 patent by adding arginine in the course of producing Reteplase.

The parties dispute three terms in the '225 patent: "tissue plasminogen activator," "pharmaceutical composition," and "incorporating," as used in the claims of the '225 patent. The claim reads as follows, with the disputed terms in bold type:

1. A method of increasing the solubility of **tissue plasminogen activator** in a **pharmaceutical composition** containing same as active principle comprising **incorporating** argininium ion in said composition, wherein said argininium ion is present in an amount effective to increase the solubility of said t-PA.

C. '502 Patent

The '502 patent claims a three-step process of purifying proteins. The parties dispute the meaning of the term "molecular sieve" as it is used in the claim of the '502 patent. The claim reads as follows, with the disputed term in bold type:

A process for purifying heterologous proteins which are expressed and deposited in insoluble refractile form in a host cell culture, which process includes the steps of:

(a) isolating said insoluble refractile heterologous protein from said host cell culture;

(b) isolating said insoluble refractile heterologous protein from said host cell culture;

(c) removing high molecular weight purities using a **molecular sieve** or high speed centrifugation techniques.

III. DISCUSSION

The construction of a patent, including terms of art within its claim, is a question of law. *See* Markman, 517 U.S. at 383-91, 116 S.Ct. at 1393-96.

[1] In resolving a claim of patent infringement, a court must "first determine the meaning and scope of the patent claims at issue, a question of law, before the factfinder may resolve whether the accused device infringes the patent claims as construed by the court, a question of fact." Storer v. Hayes Microcomputer Prod., Inc., 960 F.Supp. 498, 500 (D.Mass.1997).

[2] [3] [4] [5] In construing a patent claim, the Court looks first to the three sources of intrinsic evidence of record: the patent itself, including the claims, the specification, and if in evidence, the prosecution history. *See* Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996) (citing Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed.Cir.1995), *cert. granted,* 515 U.S. 1192, 116 S.Ct. 40, 132 L.Ed.2d 921 (1995), *aff'd,* 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996)). The first step in claim construction is an examination of the language of the claim. A construing court does not accord the specification, prosecution history, and other relevant evidence the same weight as the claim itself, but consults these sources to give the necessary context to the claim language. *See* Eastman Kodak Co. v. Goodyear Tire & Rubber Co., 114 F.3d 1547, 1555 (Fed.Cir.1997). Terms used in the claim are to be given their ordinary and customary meaning "unless another meaning is specified or evident from the patent history." Storer, 960 F.Supp. at 501 (quoting Johansson v. Rose Displays, Ltd. 924 F.Supp. 328, 330 (D.Mass.1996) (citations omitted)). The specification "acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication," Vitronics, 90 F.3d at 1582, and is the "single best guide to the meaning of a disputed term." *Id*. The patentee may, however, choose to be his or her own lexicographer and thus may use terms in a manner other than their ordinary meaning, so long as the special definition of such terms is stated in the patent specification or file history. *Id*.

[6] In interpreting the claims and specification, the construing court interprets words "as one of skill in the art at the time of the invention would understand them." Eastman Kodak, 114 F.3d at 1555. In addition, "the court should also consider the patent's prosecution history ... in order to ascertain the true meaning of the language used in the patent claim." Markman, 52 F.3d at 979-80; *see also* Standard Oil Co. v. American Cyanamid Co., 774 F.2d 448, 452 (Fed.Cir.1985) ("The prosecution history (or file wrapper) limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance.").

[7] The Court looks to extrinsic evidence to assist in construing a patent claim only if the intrinsic evidence is ambiguous. *See* Vitronics, 90 F.3d at 1583-85; Markman, 52 F.3d at 980. Thus, "[i]f a court is able to discern the meaning of a patent's claims after considering these three sources of intrinsic evidence [i.e. the patent claims, specification and prosecution history], it should not look further to expert testimony or other evidence not part of the public record...." Revlon Consumer Prod. Corp. v. L'Oreal, 170 F.R.D. 391, 393 (D.Del.1997) (citing Vitronics, 90 F.3d at 1583). Opinion evidence on claim construction, therefore, "is no better than opinion testimony on the meaning of statutory terms." Vitronics, 90 F.3d at 1585. To understand the patent, the Court may, however, consult extrinsic evidence, such as technical treatises and dictionaries in conjunction with the public record, so long as these secondary sources do not vary or contradict anything in the patent documents. Markman, 52 F.3d at 981; Revlon, 170 F.R.D. at 393 (citing Vitronics, 90 F.3d at 1584, n. 6.).

Many courts address claims construction and summary judgment in a single opinion, since the way in which a patent claim is construed often affects the determination of whether it has been infringed. *See, e.g.,* Rome v. Galilean Seafoods, Inc., 974 F.Supp. 97, 101 (D.Mass.1997) ("[I]f a court, having construed a claim, determines that the record shows no genuine dispute of fact that is material to plaintiff's assertion that the accused process infringed the patented one, summary judgment is appropriate."); Storer, 960 F.Supp. at 500 (same); MHB Indus. Corp. v. Dennis Garberg & Assoc., Inc., No. CIV A. 95-10199, 1996 WL 461592, at * 2 (D.Mass. July 25, 1996) (same), *aff'd,* 121 F.3d 726 (Fed.Cir.1997).

A. '832 Patent

The key claim construction issues for the '832 patent are the respective meanings of the terms "organically synthesized" and "gene fragments" within paragraph (c) of Claim 1.

1. ***Organic Synthesis***

[8] Genentech argues that the term "organic synthesis" as used in the '832 patent means "providing by chemical DNA synthesis, rather than by the use of the enzyme reverse transcriptase, which creates cDNA," and includes not only DNA which is directly made by chemical synthesis but also "replications (or copies) of that synthetic DNA." BM does not dispute this definition but contends that it does not adumbrate cloning methods known as site-directed mutagenesis ("SDM") and polymerase chain reaction ("PCR") which operate by enzymatic synthesis, as distinct from "organic synthesis."

a. ***Intrinsic Evidence***

Neither the '832 patent nor its specification expressly defines what is meant by the term "organic synthesis" as used in the claim. The Court, therefore, looks to the extrinsic evidence for clarification.

b. ***Extrinsic Evidence***

All the experts agree that in 1979, the term "organically synthesized" as used in the '832 patent refers to an oligonucleotide or a fragment of a gene that is "synthesized using organic chemistry," meaning that it is made by a machine or human, outside of an organism, without the use of enzymes. (Tr. 3-13 - 3-14; Tr. 2-37 - 2-38, Ex. I.) Also, Drs. Ravetch and Cepko agreed that one skilled in the art at the time of the invention would understand that a replicated synthetic fragment of DNA is still considered a fragment that is organically synthesized. (Tr. 1-60 - 1-68 and 3-17 - 3-21.) Dr. Webb did not disagree with the testimony on this point.

c. ***Claim Construction***

The term "organically synthesized" in the '832 is construed to mean the production of a oligonucleotide or fragment of a gene using organic chemistry without the use of an enzyme. It includes DNA made by replication of synthetic DNA.

2. ***Gene Fragment-Single or Double Stranded***

[9] The parties hotly dispute whether "gene fragment" as used in the '832 patent refers to single-stranded DNA, double-stranded DNA, or both. BM contends that the term, as used in the claim of the '832 patent,

should be limited to double-stranded DNA, which would exclude from the patent claim the techniques of SDM and PCR. Genentech contends that the '832 patent claim uses the term "gene fragments" to refer to both single and double-stranded DNA.

a. *Intrinsic Evidence*

The language of the claim, by itself, does not define "gene fragments" as either single or double-stranded DNA. There are numerous references to a double-stranded composite of oligonucleotides as a "gene fragment." (*See* Patent Figure 1; col. 4, 11. 40, 45, 47, 56, 58; col. 5, 11. 1, 3, 9; col. 9, 11. 63-64.) In other instances, the '832 specification depicts single-stranded DNA fragments (Figure 2) and describes single-stranded fragments as single-stranded "DNA fragments," "fragments," "primers" or "oligonucleutides," but never "gene fragments." (*See* Col. 4, 11. 39-60 and col. 10, 11. 10, 13.) Two publications cited in the prosecution history also use the term "fragment"-without the modifier "gene"-to include single-stranded synthetic DNA: K. Itakura, et al., *Expression in Escherichia Coli of a Chemically Synthesized Gene for the Hormone Somatostatin,* 198 Sci. 1056 (1977) and R. Crea, *Chemical* Synthesis of Genes *for Human* Insulin, 75 Proc.Natl.Acad.Sci. 5765 (1978).

The intrinsic evidence is ambiguous with respect to the definition of gene fragment. On the one hand, the patent specification and prosecution history expressly depict and discuss single-stranded DNA, most notably in Figure 2. This supports Genentech's argument that the term gene fragment encompasses single and double strands of DNA. On the other hand, nowhere is a single-stranded DNA fragment referred to as a "gene fragment."

b. *Extrinsic Evidence*

Because the term "gene fragment" is unclear, the Court must resort to extrinsic evidence. BM's expert, Dr. Webb, testified that as used in 1979, the term "fragment" meant either double- or single-stranded DNA, but when modified by the word "gene" in the patent, the term "gene fragment" should be construed to mean double-stranded DNA. In support of this interpretation, Webb testified that the method described in the '832 patent claim covers only a "way to cut and paste double-stranded DNA fragments of hGH [human growth hormone] together for the purpose of cloning them." (Defendants' Exhibit A at 8.) BM also points out that Genentech's own expert stated that when the term "gene fragment" is used in Step (a) of Claim 1, it refers to double-stranded DNA. (Falkinham Aff. para. 34.)

Genentech's expert, Dr. Ravetch, testified that in 1979 the term gene fragment was used "to describe a piece of DNA, whether double-stranded or single-stranded." (Tr. 1-44.) The Court-appointed expert, Cepko, also agreed that one of skill in the art in 1979 would have used the term "gene fragment" to refer to either single or double-stranded DNA, since either could carry "all the important information that you need for whatever it is you wish to do with that DNA." (Tr. 3-15.) Moreover, she testified, "you can join [a single strand] up to double strands, you can ligate it into a double-stranded molecule, you can do quite a lot with it." (Tr. 3-29.) Cepko also acknowledged, however, that attempting to carry out the steps described in the '832 patent with a single-stranded DNA fragment is "typically not done" and "is very low efficiency." (Tr. 3-32.)

3. *Gene Fragment-Length of Fragment*

With respect to the length of the synthetic fragment, BM first argues that the '832 patent is limited to ligating a significant number of synthetic codons to cDNA fragments. Its first argument rests on the term "sequence." Claim 1 of the '832 patent requires a synthetic gene fragment encoding "the remainder of the

amino acid sequence" of the known polypeptide. Quoting a standard dictionary definition of "sequence," BM argues that the synthetic gene fragment must code for more than one amino acid. The problem with this argument is that "sequence" is not one of the terms which BM flagged as a subject of the *Markman* hearing, and it is too late to raise this issue in a post-hearing brief.

BM also argues that Step (c) is practiced only if a "significant portion" of the structural gene is provided by organic synthesis. This argument rests on the prosecution history. The claims of '832 were initially rejected on February 26, 1981, pursuant to 35 U.S.C. s. 103, as being obvious in light of prior art which taught the chemical synthesis of genes that code for polypeptide hormones. Rejecting the patent claim, the examiner stated:

It would be obvious to remove the additional leader nucleotide sequences so as to provide for the transcription of active protein since microbial cells unlike eucaryotic cells cannot remove the precursor leader sequences. Where the removal results in the loss of essential parts of the coding sequence, it would be obvious to replace them by chemical synthesis such as that disclosed by Itakura et al or Crea et al.

(P.Ex. 2 at 88.)

Genentech responded by stating that the prior art taught away from the approach proposed by the examiner. *Id*. at 106. Rather, according to the inventors, one article taught that double stranded cDNA made from a mature messenger was the "material of choice" and the other noted that the size of the growth hormone prevented applying synthetic techniques. (P.Ex. 2, p. 107.) Because the prior art stated that the DNA sequence must be derived from RNA, Genentech told the Examiner that none of the prior art "proposes at any point that *any significant portion* of the structural gene itself be synthetically fashioned." *Id*. (emphasis added). Further, to refute the rejection for obviousness, the inventors distinguished other prior art as follows:

Never once is it proposed [in the prior art] that codons for the first 23 amino acids, reported as "missing" in the earlier clone, be supplied synthetically. And once further work had led to a clone comprising the entire sequence for human growth hormone, as well as additional sequences, it is nowhere proposed that codons for the superfluous protein be removed and the bioactive product expressed directly, after replacement of *any needed codons* lost in removing the presequence.

(*Id*. at 110.) (emphasis added).

BM relies on the expert testimony of Dr. Webb, who stated that small synthetic fragments of DNA, which he called linkers, were used in the prior art, and that methodologically, the claimed invention "differed from the prior art only in that it relied on the 'marriage' of a cDNA fragment made by the enzyme reverse transcriptase with a long, organically synthesized DNA fragment." (D.Ex. A para.para. 17-19.)

While Dr. Webb may well be correct in describing prior art, an analysis of the prosecution history as a whole does not support BM's reliance on the doctrine of prosecution history estoppel. The thrust of Genentech's argument to the examiner is that none of the prior art taught any organic synthesis of the missing portion of the structural gene, regardless of whether the missing portion was significant or just a missing codon. Steps (a) and (b) state that the first gene fragment procured by reverse transcription is subject to no size limitation other than that it be less than the entire coding sequence. Moreover, the inventors described the claims which were amended to deal with the examiner's indefiniteness concern as claims "which now encompass every situation in which any portion of the subject genes (albeit less than all

of it) is derived by reverse transcription from messenger RNA." (*Id*. at 101.) Accordingly, the Court concludes that Genentech is not bound to the limitation that a "significant portion" of the structural gene must be achieved through organic synthesis.

c. *Claim Construction*

Based on the patent specification and prosecution history, the Court construes the term "gene fragment" in the '832 patent claim to refer to either single or double-stranded DNA, of any length.FN2

FN2. BM argues that such a construction leaves unresolved the issue of enablement because the '832 does not enable the use of single strand DNA without undue experimentation. *See* Genentech, Inc. v. Novo Nordisk, 108 F.3d 1361, 1365 (Fed.Cir.1997) (invalidating patent for failure of specification to enable practice of claimed method), *cert. denied,* 522 U.S. 963, 118 S.Ct. 397, 139 L.Ed.2d 310 (1997); Genentech, Inc. v. Wellcome Foundation, Ltd., 29 F.3d 1555, 1564 (Fed.Cir.1994) (refusing to construe patent in way that would require undue experimentation). BM also argues that SDM and PCR do not infringe the patent claims because they operate by enzymatic synthesis. Those arguments will have to await another day.

B. '225 Patent

The '225 patent claims a method for increasing the solubility and stability of t-PA by incorporating argininium. The key issues for claims construction are the definitions of the terms "tissue plasminogen activator," "pharmaceutical composition," and "incorporating."

1. *Tissue Plasminogen Activator*

[10] Genentech contends that the term "tissue plasminogen activator" as used in Claim 1 of the '225 patent means "native human tissue plasminogen activator or biologically active human tissue plasminogen equivalents, where 'biologically active human tissue plasminogen activator equivalents' means tissue plasminogen activators or analogs which are derived from native human t-PA gene and meet all of the following functional characteristics ... (a) cleave plasminogen to plasmin; (b) bind to fibrin; and (3) share immunological properties of native human t-PA."

BM argues that the term "tissue plasminogen activator" was decisively defined in Genentech, Inc. v. Wellcome Foundation, Ltd., 29 F.3d 1555, 1565-67 (Fed.Cir.1994). The *Wellcome* Court, after reviewing two Genentech t-PA patent claims and patent specifications, concluded that the phrase "human tissue plasminogen activator" in those claims meant "natural t-PA" or "t-PA produced through recombinant DNA technology but having the same structure as natural t-PA." *Id*. at 1565; *see also* Genentech v. Chiron Corp., 112 F.3d 495, 501 (Fed.Cir.1997) (pointing out that it construed the term "human tissue plasminogen activator in the context of the claims of the patent at issue in that case."). With respect to the functional definition which is substantially the same as the definition in the '225 patent, the Court noted:

There may also be a problem with satisfaction of the definiteness and description requirements of 35 U.S.C. s. 112 in relation to these other definitions, especially *the fourth functional definitions*. The DNA isolate which is the subject of the '075 and '330 claims is itself defined in functional terms, i.e., as any sequence that encodes human t-PA. A conclusion that the phrase "human tissue plasminogen activator" is also defined in functional terms would give rise to a definiteness problem because a competitor could not then reasonably determine that DNA sequences are within the scope of the claims and which are not. It would

also give rise to a problem with the description requirement because the specification does not even remotely describe all the DNA sequences that encode the proteins within the scope of the functional definition.

Id. at 1565 n. 25 (emphasis added); *see also* Fiers v. Revel, 984 F.2d 1164, 1171 (Fed.Cir.1993).

The court in *Wellcome,* however, was not construing the claims in Genentech's '225 patent, which is the limited purpose of this proceeding. As Genentech pointed out, the *Wellcome* court construed the patents in light of the knowledge in 1982, and the '225 patent was filed in 1985. Moreover, the focus of the patents differ. The '225 patent is directed to a method of increasing the solubility of t-PA while the *Wellcome* patents claimed human t-PA itself, as well as the expression vector and cell culture producing it. The troublesome question as to whether the functional definition in the '225 patent is "hopelessly overbroad," id. at 1564, and meets the requirements of 25 U.S.C. s. 112, is not appropriate for a *Markman* hearing.

a. *Intrinsic Evidence*

The term "tissue plasminogen activator" is not defined in the '225 claim itself. The '225 patent specification, however, provides the following definitions:

The terms "human tissue plasminogen activator," "human t-PA," or "t-PA" denotes human extrinsic (tissue type) plasminogen activator, produced, for example, from natural source extraction and purification (see Collen, et al., supra), and by recombinant cell culture systems as described herein. Its sequence and characteristics are set forth, for example, in European Application Publ. No. 93619 (published 9 Nov. 1983) based upon a first filing on 5 May 1982, incorporated herein by reference. See also European Patent Application Publication No. 41766 (published 16 Dec. 1981) based upon a first filing of 11 June 80 and Riijken et al., Journal of Biol. Chem. 256, 7035 (1981), also incorporated herein by reference.

The terms likewise cover biologically active human issue plasminogen activator equivalents, different in one or more amino acid(s) in the overall sequence, or in glycosylation patterns, which are though [sic] to be dependent on the specific culture conditions used and the nature of the host from which the tissue plasminogen activator is obtained.

('225 patent, col. 3, l. 65, col. 4, ll. 9-16.)

The '225 specification incorporates, by reference, the "sequence and characteristics" of t-PA set forth in European Patent Application Publn. No. 93619 ('225 Patent, col. 4, ll. 1-4.) That application provided a "functional definition" of human t-PA: "it is capable of catalyzing the conversion of plasminogen to plasmin, binds to fibrin, and is classified as a t-PA based on immunological properties." (European Patent Application Publn. No. 93619.) The '225 patent specification also incorporates, by reference, Riijken, et al., *Journal of Biological Chemistry* 256, 7035 (1981), an article that defines human t-PA by the same three functional characteristics. ('225 patent, col. 4, l. 8.)

The dispute, it seems, focuses on whether the term tissue plasminogen activator in Claim 1 embraces equivalents with certain functional characteristics. The intrinsic evidence unambiguously answers yes. The term t-PA expressly covers "biologically active human tissue plasminogen equivalents" as described at Col. V, line 11-16, with the functional characteristics set forth in the European patent application.

b. *Claim Construction*

The Court construes the meaning of the term "tissue plasminogen activator," as used in Claim 1 of the '225 patent, to mean native human t-PA, whether produced from natural source extraction or recombinant cell culture systems described in the patent, as well as certain described biologically active human tissue plasminogen activator equivalents which (i) are capable of catalyzing the conversion of plasminogen to plasmin; (ii) bind to fibrin, and; (iii) share basic immunological properties of native t-PA.

2. *Pharmaceutical Composition*

[11] Genentech contends that the term "pharmaceutical composition" means "a stable composition suitable for administration into patients, for example, a solution designed for parenteral administration or a lyophilized [freeze-dried] form thereof." BM contends that the term "pharmaceutical composition" is defined as a "highly purified preparation."

The relevance of the term is that BM first adds arginine in the production and purification of Reteplase to the refolding solution, which is "at least six steps before Reteplase is in the pharmaceutical composition stage."

a. *Intrinsic Evidence*

The '225 patent specification provides: "Pharmaceutical compositions must be stable for appropriate periods of time, must be acceptable in their own right for administration to humans, and must be readily manufacturable." (Col.1, 11.57-60.) It also states:

A particular method for preparing a pharmaceutical composition of t-PA hereof comprises employing purified (according to any standard protein purification scheme) t-PA in any one of several known buffer exchange methods, such as gel filtration. This preferred method was used to isolate and purify the t-PA used as starting material in the stability and solubility studies.

(Col.3, 11.37-41.) In each example given in the '225 patent, and in the methods for production of Figures 1-3, purified t-PA was used. (Cepko Report, at 7.) The preferred embodiment in a specification is helpful in construing the terms of a patent, although not conclusive. *See* Vitronics, 90 F.3d at 1583.

b. *Claim Construction*

Because the patent specification is the "single best guide to the meaning of a disputed term," Vitronics, 90 F.3d at 1582, and the term is clearly defined in the '225 patent specification, the Court has no need to turn to the extrinsic evidence. Therefore, the Court construes the term "pharmaceutical compositions" to mean those that are stable for appropriate periods of time, acceptable in their own right for administration to humans, and readily manufacturable. A pharmaceutical composition is comprised of purified t-PA.

3. *Incorporating*

[12] Genentech contends that the term "incorporating" should be given its plain English meaning. It argues that the phrase "incorporating argininium ion in said composition" means "the pharmaceutical composition contains at least argininium ions and tissue plasminogen activator, or analogs, however and whenever incorporated." (Genentech Memo at 14.) BM contends that the phrase "incorporating" refers to "adding

arginine to a pharmaceutical composition." Specifically, BM argues that because the '225 patent is a "method" patent, rather than a composition patent, the term "incorporating" must be construed as a "*process* for increasing the solubility of t-PA in a pharmaceutical composition by adding arginine."

This issue is relevant because the BM's product, BM 06.022, "first encounters argininium ions when it is not purified" and "when it is not native in its folding pattern." (Cepko report at 7.) BM thus uses argininium ions for the purpose of refolding denatured, but soluble, t-PA. BM does not remove the argininium ions from its product and, therefore, Reteplase contains argininium ions in the pharmaceutical composition that is administered to patients. (Cepko report at 8.)

a. *Intrinsic Evidence*

The term "incorporating" is not expressly defined in the '225 patent. To begin with, the plain English language meaning of "incorporating" includes the following definitions:

to put or introduce into a body or mass as an integral part or parts; to take in or include as a part or parts, as the body or a mass does; to form or combine into one body or uniform substance, as ingredients; to unite or combine so as to form one body; combined into one body, mass, or substance.

Random House Unabridged Dictionary 968 (2d ed.1993). The word "incorporating" directly follows the open-ended term "comprising." The Federal Circuit has defined "comprising" as follows: " 'Comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." Chiron, 112 F.3d at 501.

The '225 specification states that the purpose of incorporating argininium ions in a buffer composition is to increase the "stability and solubility characteristics for the t-PA component." ('225 Patent, col. 1, 11. 14-16; col. 2, 11. 12-14; 18-19.) There is no mention in the '225 patent of using argininium ions to allow the refolding of denatured t-PA.

The '225 patent does not explicitly define the exact point at which t-PA is placed in the solution ("buffer") with argininium ions. Nonetheless, in "each example given in the '225 patent, and in the methods for production of Figures 1-3, purified t-PA was used." (Cepko report at 7.)

The prosecution history, likewise, provides guidance. In the patent application, for example, Genentech states that the invention is based on the discovery that the "inclusion of arginine (as argininium ion) in a pharmaceutically acceptable composition" of t-PA "significantly increases the stability and solubility of t-PA...." (Patent application at p. 3, 11. 14-18; page 5, 11. 15-16.) Finally, Genentech's March 13, 1990 preliminary amendment to the '225 application states that "the claim of the present invention is directed to increasing the solubility of t-PA via the addition of argininium ion as such." (March 13, 1990 amendment, p. 2.)

The grammatical structure of the claim itself contains a key clue to the meaning of incorporate. To construe a claim, courts must look at the language as a whole and consider the grammatical structure and syntax. Chiron, 112 F.3d at 500. The term cannot simply mean that the composition contains argininium because that construction would make "incorporating" and "comprising" redundant. Also, if "incorporating" meant containing, without connecting a sequence of events, there would be no need for the phrase "in said composition."

b. ***Claim Construction***

Based on the language of the claim, the purpose of the invention, the specification, and the prosecution history, I conclude that the term "incorporating" refers to adding argininium to a pharmaceutical composition of t-PA.

C. '502 Patent

[13] The '502 patent claims a method for extracting desired proteins from refractile bodies and separating these proteins from high molecular weight contaminants by use of a molecular sieve or high speed centrifugation. ('502 patent, Col. 4, 11. 31-37.) The key contested term in the claims construction is the term "molecular sieve," as used in paragraph (c).

Genentech contends that the term "molecular sieve" is "a general term used to describe various techniques for separation based on size," including a filter, gel electrophoresis or gel permeation chromatography (also known as gel filtration). BM contends that the term "molecular sieve" refers only to a gel permeation chromatography or gel filtration, and does not include BM's use of "dead-end filtration."

1. ***Intrinsic Evidence***

BM relies primarily on intrinsic evidence to support its argument. In a section headed "Detailed Description of the Invention," the specification of the '502 patent states:

(A) Definitions: .... There are abbreviations and descriptions conventionally used with regard to particular techniques that are used in this invention, and for convenience these will be described briefly here:

Gel permeation chromatography or gel filtration is a commonly used purification technique which discriminates between molecules according to their size. This is also frequently referred to as a **"molecular sieve."** By suitable selection of the gel, almost any range can be selected for. Molecules which are large enough to be excluded from the gel pores are passed untreated through a column containing the gel; smaller molecules are fractionated by the column.

(Col. 6, 11. 8-10; Col. 8, 11. 30-38.) (emphasis added). In the "Definitions" section, defined terms generally appear in quotation marks. The specification later states:

In carrying out the removal of high molecular weight impurities through gel filtration, a column containing a molecular sieve, such as, for example, Sephacryl S-300 is equilibrated in a suitable buffer and the solution containing the heterologous protein passed through the column.

(Col.14, 11.1-14.) and again:

Use of gel permeation chromatography as a first chromatographic step in a commercial purification process for protein, i.e. carrying out gel permeation prior to, for example, ion exchange chromatography, is unusual.

(Col.14, 11.19-25.) Finally, the specification refers to the separation of high weight contaminants as the "gel filtration step," (Col.21, 1.13.) and describes an "optimal subsequent purification regime which has, as a primary step, gel filtration or high speed centrifugation." (Col.22, 11.4-7.)

The prosecution history also refers to a "gel filtration step" and a "size-discriminating gel permeation molecular sieve." (Prosecution History, at pp. 25-6, 40.)

Genentech argues that in 1982, several different types of molecular sieves were known and in common use by protein biochemists and chemical engineers. There are two extrinsic sources of evidence. First, court-appointed expert, Dr. Cepko, testified that the term "molecular sieve" meant, to one skilled in the art at the relevant time in 1982, any technique that separates molecules based on size, including filters. (Tr. 3-35 3-37.) Second, Genentech introduced into evidence contemporaneous bioprocessing literature to support its argument that molecular sieve means a size-based separator and that ultra filtration membranes and depth filters have been described as molecular sieves in the relevant time period. (*See, e .g.,* Pl.Ex. 28, 31.) The defendants read into evidence a portion of the book by Robert Scopes, Protein Purification *Principles and Practice,* which states, for the relevant time period, under the heading "gel filtration":

"Several other names for this method have been put forward, including ' *gel permeation* ' and ' *molecular sieving*.' However, the use of the term ' *gel filtration* ' is now so widespread and generally recognized that it will be used here. This name is unfortunate, since the procedure does not depend on the material used being a true gel, and it is not really filtration."

(Tr. 3-41; Defendants' Exhibit U, at p. 368.)

Although the meaning of "molecular sieve" to those skilled in the art encompassed more than gel filtration in 1982, Genentech cannot use extrinsic evidence to vary an unambiguous, defined term in quotations in the patent. Patent applications must disclose their inventions adequately. *See* North Am. Vaccine, Inc. v. American Cyanamid Co., 7 F.3d 1571, 1576 (Fed.Cir.1993) ("A patent application cannot disclose and claim an invention narrowly and then, in the course of an infringement suit, argue effectively that the claims should be construed to cover that which is neither described nor enabled in the patent."), *cert. denied,* 511 U.S. 1069, 114 S.Ct. 1645, 128 L.Ed.2d 365 (1994). Genentech claims that gel filtration or gel permeation is provided only as an example or preferred embodiment of a molecular sieve. Although references to a preferred embodiment are not claim limitations, a court may look to a preferred embodiment in a specification for assistance in construing its claim. *See* Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1575 (Fed.Cir.1997).

Nothing in the patent specification or prosecution history supports Genentech's claim that the inventors, or the PTO, envisioned the term "molecular sieve" to mean anything other than gel permeation or gel filtration. *Cf.* Wellcome, 29 F.3d at 1564 ("An appropriate method for resolving the issue [when the specification contains diverse definitions of a given term] is to avoid those definitions upon which the PTO could not reasonable have relied when it issued the patent."); *cf.* Novo, 108 F.3d at 1366 ("It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.").

2. *Claim Construction*

The term "molecular sieve" as used in the '502 patent is construed to mean gel permeation or gel filtration techniques which separate molecules based on size.

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