NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Plaintiff-Appellant,

v.

GENENTECH, INC.,
Defendant-Appellee,

and

BIOGEN IDEC INC.,
Defendant-Appellee,

2011-1397

Appeal from the United States District Court for the Northern District of California in Case Nos. 08-CV-4909 and 09-CV-4919, Judge Susan Illston.

Decided: March 22, 2012

WILLIAM E. SOLANDER, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for plaintiff-appellant. With him on the brief were DOMINICK A.

CONDE, NINA SHREVE, JOSHUA A. DAVIS and CHARLOTTE C. JACOBSEN.

CHARLES K. VERHOEVEN, Quinn Emanuel Urquhart & Sullivan, LLP, of San Francisco, California, argued for both defendants-appellees. With him on the brief were VICTORIA F. MAROULIS, ERIC E. WALL and GABRIEL S. GROSS. Of counsel on the brief were DONALD R. WARE, CLAIRE LAPORTE, JEREMY A. YOUNKIN and MARCO J. QUINA, Foley Hoag, LLP, of Boston, Massachusetts.

Before NEWMAN, LOURIE, and PROST, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Plaintiff-Appellant Sanofi-Aventis Deutschland GmbH ("Sanofi") appeals from the decision of the United States District Court for the Northern District of California granting summary judgment of noninfringement of its U.S. Patents 5,849,522 ("the '522 patent") and 6,218,140 ("the '140 patent") in favor of Defendant-Appellees Genentech, Inc. ("Genentech") and Biogen Idec Inc. ("Biogen"). *Sanofi-Aventis Deutschland GmbH v. Genentech, Inc.*, Nos. C 08-4909 SI, C 09-4919 SI, 2011 U.S. Dist. LEXIS 28334, 2011 WL 839411 (N.D. Cal. Mar. 7, 2011) ("*Final Judgment*"). Because we conclude that the district court did not err in its judgment, we *affirm*.

I. BACKGROUND

The '522 and '140 patents, assigned to Sanofi, arose from the same patent family and share the same single-page written description, which discloses enhancer ele-

ments derived from human cytomegalovirus ("HCMV").[1] Enhancers are discrete segments of DNA capable of enhancing the expression of one or more functionally associated gene(s) by upregulating transcription—the process of synthesizing RNA from a DNA template. Generally speaking, enhancers recruit and locally concentrate certain proteins needed for transcription, leading to increased production of RNA from associated genes. The resulting abundance of RNA, once translated, yields correspondingly abundant protein expression. Enhancers are often found immediately upstream of enhancer-activated genes, but they can also function if placed downstream or even thousands of base pairs away from a gene. Once identified, enhancers often have considerable practical utility and have been adopted in the biotechnology and pharmaceutical industries to boost production efficiency for protein-based products. For example, by linking an enhancer to a gene encoding a biologic drug, researchers can often significantly improve yields from cells expressing that gene.

The enhancer described in the '522 and '140 patents—first discovered within non-coding DNA located upstream of the highly expressed HCMV major immediate early ("IE") gene—is particularly powerful and versatile, demonstrating activity across a wide spectrum of eukaryotic cell types. The '522 patent claims methods of using the HCMV IE enhancer to increase expression of a gene in a mammalian cell, and the '140 patent claims isolated HCMV IE enhancers, plasmid DNAs comprising an

[1] Through serial continuation applications, the '522 and '140 patents both claim priority from German Patent Application No. 34 31 140.8, filed August 24, 1984. The '522 patent was filed on June 6, 1995, and issued on December 15, 1998, and the '140 patent was filed on November 9, 1994, and issued on April 17, 2001.

HCMV IE enhancer operatively linked to a heterologous gene, and eukaryotic host cells transformed with such plasmids.

In 2008, Sanofi brought an action for infringement of the '522 and '140 patents, alleging that Appellees made use of an infringing HCMV IE enhancer in producing the antibody-based pharmaceuticals Rituxan® and Avastin®. In turn, Appellees filed a declaratory judgment complaint alleging invalidity and noninfringement, and the two actions were consolidated in the United States District Court for the Northern District of California. The district court held *Markman* proceedings and construed several disputed claim terms in each patent. *Sanofi-Aventis Deutschland GmbH v. Genentech, Inc.*, Nos. C 08-4909 SI, C 09-4919 SI, 2010 U.S. Dist. LEXIS 68875, 2010 WL 2525118, at *4–15 (N.D. Cal. June 23, 2010) ("*Claim Construction Order*"). In light of the claim construction decision, Appellees moved for summary judgment of noninfringement, which the district court granted. The court concluded that Appellees did not infringe the '522 or '140 patents literally or under the doctrine of equivalents in producing Rituxan® and Avastin®. *Final Judgment*, 2011 WL 839411, at *4–15.

Sanofi appealed, and we have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

We review the district court's grant of summary judgment of noninfringement and its underlying claim construction *de novo*. *Laryngeal Mask Co. Ltd. v. Ambu A/S*, 618 F.3d 1367, 1370 (Fed. Cir. 2010). Summary judgment is appropriate when "there is no genuine dis-

pute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a).

A. The '522 Patent

Sanofi asserted claims 1 and 2 of the '522 patent. Independent claim 1 is representative for purposes of this appeal and reads as follows:

> 1. A method to increase expression of a gene in a mammalian cell comprising *inserting* into the mammalian cell an *isolated DNA enhancer* consisting of *DNA from the upstream region of the major immediate early (IE) gene of human cytomegalovirus (HCMV)* and a heterologous gene that is to be expressed, wherein the DNA from the upstream region of the IE gene of HCMV is the only HCMV material to which the mammalian cell is exposed.

'522 patent col.2 l.63 – col.3 l.3 (emphases added).[2]

In the district court, the parties disputed the meanings of "isolated DNA enhancer" and "DNA from the upstream region of the major immediate early (IE) gene of human cytomegalovirus (HCMV)." In resolving those issues, the district court construed "isolated DNA enhancer" to mean

[2] Claim 2 depends from claim 1, imposing further limitations on the DNA that can constitute the isolated DNA enhancer recited in claim 1. *See* '522 patent col.3 ll.4–8. Because we agree with the district court that Appellees do not infringe claim 1, we need not separately address claim 2.

> a DNA sequence, *separated* by human intervention *from the promoter DNA in its original source*, that (1) strongly stimulates transcription of a linked gene, (2) functions independent of orientation, and (3) functions even if located long distances upstream or downstream relative to the initiation site of the linked gene.

Claim Construction Order, 2010 WL 2525118, at *5 (emphases added). The district court next construed "DNA from the upstream region of the major immediate early (IE) gene of human cytomegalovirus (HCMV)" as "DNA from the region that is upstream of the transcription start site of the major IE gene of HCMV." *Id.* at *7. On the issue of infringement, the district court held that Appellees did not infringe the '522 patent because, *inter alia*, Appellees do not practice the step of "inserting" an isolated DNA enhancer into a mammalian cell. *Final Judgment*, 2011 WL 839411, at *4–6.

1. Claim Construction

a. The Isolated DNA Enhancer

On appeal, Sanofi argues that the district court erred by defining "isolated DNA enhancer" to require the enhancer to be "separated . . . from the promoter DNA in its original source." *Claim Construction Order*, 2010 WL 2525118, at *5. Sanofi argues that the claimed "isolated DNA enhancer" can include the native HCMV promoter but concedes that it need not, pointing out that the '522 patent's specification teaches that the HCMV enhancer can be used with or without the HCMV IE promoter. *See* '522 patent col.2 ll.6–10, 43–56. Appellees respond that Sanofi disclaimed enhancer fragments that include the HCMV IE promoter during prosecution and that the

disclosure excludes the promoter from its discussion of enhancer-active elements. We agree with the district court that the intrinsic evidence does not support Sanofi's construction.

We have held that an otherwise broadly defined term can be narrowed during prosecution through arguments made to distinguish prior art. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (en banc). In this case, the applicants made such a disclaimer during prosecution of U.S. Patent Application No. 07/170,140—an ancestor of the application that eventually issued as the '522 patent—to overcome obviousness rejections against then-pending claims that recited an "isolated enhancer." Specifically, the examiner had cited two references (Thomsen and Jahn) that disclose HCMV-derived DNA sequences encompassing the HCMV IE enhancer and promoter regions. In a response dated March 14, 1988, the applicants distinguished the cited art, as follows:

> [N]either of these primary references teaches the preparation of an isolated enhancer region as defined by the pending claims. . . . Thomsen et al. expressly discusses *promoter* sequences . . . . [Jahn] isolates and characterizes a variety of clones and illustrates several maps. The reference does not appear to isolate an enhancer sequence . . . .

J.A. 806–07 (emphasis in original).

Thus, the applicants distinguished their isolated enhancer from the cited references, and such statements amount to "a clear and unmistakable disavowal of scope during prosecution" of the '522 patent. *Purdue Pharma L.P. v. Endo Pharms. Inc.*, 438 F.3d 1123, 1136 (Fed. Cir.

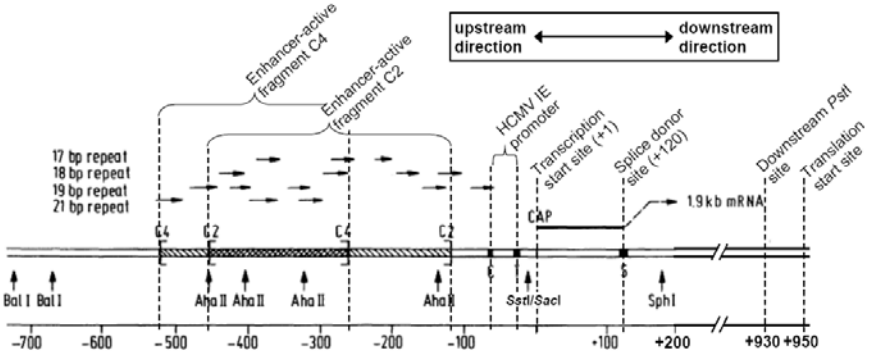
2006); *see also Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 997–98 (Fed. Cir. 2006). Because Thomsen and Jahn disclose the entire HCMV IE regulatory region, including the claimed enhancer sequences, the applicants cast those references as general disclosures that failed to describe or isolate the HCMV enhancer from its native context within the surrounding viral sequences. Moreover, the applicants underscored the presence of HCMV IE promoter sequences in Thomsen to distinguish that reference from the "isolated enhancer" recited in the pending claims. Hence, their claims must be interpreted to refer to the enhancer separated from the promoter, and we agree with the district court that the term "isolated DNA enhancer" requires an enhancer separated from the promoter DNA in its original source.

b. The Upstream Region of the IE Gene

In addition, Sanofi alleges error in the construction of the term "DNA from the upstream region of the major immediate early (IE) gene of human cytomegalovirus (HCMV)," which the district court interpreted to mean "DNA from the region that is upstream of the *transcription* start site of the major IE gene of HCMV." *Claim Construction Order*, 2010 WL 2525118, at *7 (emphasis added). Sanofi contends that the term "DNA from the upstream region of the major immediate early (IE) gene of human cytomegalovirus (HCMV)" should be construed to mean "DNA from upstream of the *translation* start site of the major IE gene of HCMV." According to Sanofi, the specification discloses the use of HCMV enhancers including portions of viral DNA extending beyond the transcription start site to the HCMV splice donor site at +120 or the downstream *Pst*I site at approximately +930. *See* '522 patent col.2 ll.6–10, 44–56. To include those features, Sanofi argues, the claimed "upstream region of the major

immediate early (IE) gene" must encompass the transcribed, but untranslated, region spanning the transcription and translation start sites of the HCMV IE gene at +1 and approximately +950, respectively. We disagree.

A diagram of the HCMV IE gene, adapted from figure 1a of the '522 patent and marked to emphasize relevant points of reference, is shown below:



Claim 1 recites the method of using an isolated DNA enhancer that consists of "DNA from the *upstream region* of the [HCMV IE gene]," and the specification uses consistent language in describing the HCMV enhancer's position as "located in the *upstream region* of the [HCMV IE gene]." *Id.* [57] (emphasis added); *see also id.* col.1 ll.14–17. But the specification describes the location of the +120 splice donor site differently, with the key phrase "upstream region" notably absent. Rather, the specification describes the +120 splice donor sequence as the "splice donor consensus sequence *of the IE gene*." *Id.* col.2 ll.8–9 (emphasis added). Thus, while the +120 splice donor site is indeed part of the IE gene, the specification reserves the "upstream region" label from its discussion of the splice donor site, indicating that the claim term "DNA from the upstream region of the [HCMV IE gene]" specifies a distinct portion of the broader IE gene that excludes

the splice donor site (+120), the downstream *Pst*I site (+930), and the translation start site (+950).[3]

We therefore reject Sanofi's contention that the downstream end of the "upstream region" recited in claim 1 extends to the translation start site of the IE gene, and we affirm the construction adopted by the district court.

2. Infringement

The district court held on summary judgment that Appellees do not infringe claims 1 or 2 of the '522 patent because, among other reasons, Appellees do not practice the required step of "inserting" an isolated DNA enhancer into a mammalian cell. *Final Judgment*, 2011 WL 839411, at *4–6. We agree.

In the district court, the parties stipulated that "inserting," as used in the '522 patent, means "putting or introducing into." *Id.* at *4. Furthermore, the parties agree that Appellees derived the cell lines used to produce Rituxan® and Avastin® by inserting foreign DNA into mammalian cells, but also that those acts occurred before the '522 patent issued in 1998 and therefore cannot constitute infringement. *Id.*; *see Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359–60 (Fed. Cir. 2007). Sanofi nonetheless urges that Appellees literally perform the requisite infringing acts by propagating their existing cell lines, thereby "inserting" the foreign DNA into daughter cells with each round of mitosis. The '522 patent only teaches inserting foreign DNA via transfection, however, and does not discuss cell division as a

[3] An "upstream region" that excludes the splice donor site at +120 must also exclude sites such as the *Pst*I site and the translation start site located even further downstream.

means for introducing foreign DNA. *See* '522 patent col.1 l.42, col.2 ll.20, 39. More fundamentally, Sanofi's argument contradicts basic scientific understanding and common sense. During mitosis, existing chromosomes replicate inside a cell, which then splits to produce identical daughter cells containing the same DNA as the parent. DNA replicated during mitosis is not "put or introduced into" a cell; it is already there.

We therefore agree with the district court that there is no genuine issue of material fact that Appellees do not literally infringe the asserted claims of the '522 patent. Furthermore, we agree with the district court that Appellees do not infringe under the doctrine of equivalents because "inserting" extraneous DNA into a cell differs substantially from routine mitotic propagation, and a finding of equivalence would vitiate the claim term "inserting." *See Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1355 (Fed. Cir. 2010). Because our affirmance of the district court's conclusion that the claims are not infringed on the ground that Appellees do not insert enhancer DNA into a mammalian cell is sufficient to dispose of Sanofi's infringement allegations regarding the '522 patent, we need not review the application of the claim terms "isolated DNA enhancer" and "DNA from the upstream region of the [HCMV IE gene]" to Appellees' activities. As noted above, however, we have affirmed the district court's construction of those terms.

B. The '140 Patent

Sanofi asserted claims 42–45 of the '140 patent. Claims 42 and 45 each claim a "recombinant DNA plasmid" comprising an enhancer-active DNA molecule isolated from the HCMV IE gene operatively linked to a

heterologous gene. Claims 43 and 44 claim eukaryotic host cells transformed with such a plasmid.

Regarding the pivotal claim term "recombinant DNA plasmid," the parties offered conflicting interpretations of the word "plasmid." That term is absent from the written description of the '140 patent. The district court looked to U.S. Patent 5,168,062 ("Stinski") as important intrinsic evidence of the meaning of "plasmid," as the term first appeared in the '140 patent in claims copied from Stinski and because the examiner cited Stinski as the basis of rejections during prosecution of the '140 patent. *Id.* at *10–11. In relevant part, Stinski defines a "plasmid" as "a closed ring," "not linked to the chromosome of the host cell." Stinski col.3 ll.1–8, 19. Accordingly, the district court adopted Biogen's proposed construction defining "plasmid" to mean a "circular, extrachromosomal molecule." *Claim Construction Order*, 2010 WL 2525118, at *11.

Having adopted Biogen's proposed definition of "plasmid," the district court then held that Appellees do not infringe the asserted claims because the heterologous DNA used to produce Rituxan® and Avastin® is linear and integrated rather than circular and extrachromosomal. *Final Judgment*, 2011 WL 839411, at *11–14.

1. Claim Construction

Sanofi argues that the district court erred in its construction of "plasmid," contending that the ordinary meaning of the term includes both circular and linear forms and that the district court incorrectly treated Stinski as controlling intrinsic evidence. Sanofi maintains that "plasmid" should be defined more broadly as a sequence of DNA "that may be linear or circular and that

may exist in an extrachromosomal state or integrated into a cell's chromosome."

As noted, the word "plasmid" appears nowhere in the written description of the '140 patent; the term first appeared when the applicants copied claims from Stinski during prosecution. But the '140 patent discloses two examples of plasmids, both of which are circular and extrachromosomal, *see* '140 patent col.2 ll.45–56, and that evidence from the patent itself accords with the district court's construction. Furthermore, the district court correctly recognized Stinski, which the examiner cited during prosecution, as sufficiently intrinsic evidence for purposes of interpreting the '140 patent. *See Phillips*, 415 F.3d at 1317 ("The prosecution history, which we have designated as part of the 'intrinsic evidence,' consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent."). Given the scant insights offered within the '140 patent concerning the meaning of "plasmid," the consistent teachings of Stinski, and the lack of other countervailing evidence from the intrinsic record, we discern no error in the district court's construction.

Sanofi complains that the district court's construction unduly limits the ordinary meaning of the term "plasmid," offering expert testimony and various other pieces of extrinsic evidence that it claims more accurately reflect the perspective of those skilled in the art at the time of the invention. But Appellees counter Sanofi's arguments with a contrary array of extrinsic evidence and note that the available intrinsic evidence supports the district court's construction. We cannot agree that Sanofi's submissions outweigh the intrinsic evidence. As we held in *Phillips*, "extrinsic evidence may be useful to the court, but it is unlikely to result in a reliable interpretation of

patent claim scope unless considered in the context of the intrinsic evidence." *Id.* at 1319. Regardless of what meaning may be attributed to the term "plasmid" in other contexts and at other times, its meaning in the instant patent, having an effective filing date of August 24, 1984, is as a circular, extrachromosomal piece of DNA.

Sanofi also argues that the district court's construction would render claim 43 "internally inconsistent" because that claim recites "[a] eukaryotic host cell *transformed* with a recombinant DNA plasmid." '140 patent col.5 ll.8–9 (emphasis added). Sanofi argues that "the ordinary understanding of a transformed cell is one in which the plasmid is *integrated*," that is, linearized and integrated into a host chromosome. Br. for Plaintiff-Appellant at 37. The parties agreed before the claim construction hearing, however, that "transformed" means "altered to include foreign DNA," J.A. 650, and that definition can indicate the result of a transient transfection with circular, extrachromosomal DNA as well as indicating the integration of extraneous linear DNA into a chromosome, but it does not compel Sanofi's interpretation. Furthermore, the only such "transformed" cells described in the '140 patent resulted from transient transfection, not integration. *See* '140 patent col.2 ll.53–56. Sanofi's argument is therefore unavailing.

We have considered Sanofi's remaining arguments and find them unpersuasive. Accordingly, we affirm the district court's construction of "plasmid" as a "circular, extrachromosomal molecule."

2. Infringement

The district court held on summary judgment that Appellees do not infringe claims 42–45 of the '140 patent

literally or under the doctrine of equivalents. On appeal, Sanofi challenges only the holding of noninfringement under the doctrine of equivalents, arguing that the district court incorrectly conflated literal infringement with the doctrine of equivalents and mischaracterized the function of the claimed plasmid for purposes of the equivalents analysis. Sanofi maintains that the differences between the claimed circular extrachromosomal plasmids and Appellees' linear, integrated DNAs are insubstantial because both provide the same genetic information and therefore achieve the same heterologous protein expression in the same way.

We agree with the district court that Sanofi cannot rely on the doctrine of equivalents because doing so would vitiate the "plasmid" limitation of each asserted claim. Patentees may not assert "a theory of equivalence [that] would entirely vitiate a particular claim element." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 39 n.8 (1997). Sanofi argues that the claimed "recombinant DNA plasmid" provides "a fixed arrangement of those pieces of DNA required for gene expression by the cell's transcriptional machinery," and that linear or circular DNA can perform this function in the same way to achieve the same result. Br. for Plaintiff-Appellant at 44–45. But such a theory of equivalence of the claimed "recombinant DNA plasmid" focuses on the functions attributable to "recombinant DNA" and ignores the "plasmid" requirement. Although recombinant DNA in both linear and integrated, or circular and extrachromosomal, forms are capable of providing a template for gene expression, the claims call for achieving that function with a "plasmid"—defined here as a circular, extrachromosomal molecule.

To find equivalence in this situation would be to read the "plasmid" element out of the claims entirely, which the district court correctly declined to do. *See SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1347 (Fed. Cir. 2001) ("[I]f a patent states that the claimed device must be 'non-metallic,' the patentee cannot assert the patent against a metallic device on the ground that a metallic device is equivalent to a non-metallic device."). The Appellees were therefore entitled to summary judgment of noninfringement of the asserted claims of the '140 patent.

III. CONCLUSION

Accordingly, we *affirm* the final judgment of the district court.

AFFIRMED