United States Court of Appeals for the Federal Circuit

BILLUPS-ROTHENBERG, INC.,
Plaintiff-Appellant,

v.

ASSOCIATED REGIONAL AND UNIVERSITY PATHOLOGISTS, INC. (DOING BUSINESS AS ARUP LABORATORIES) AND BIO-RAD LABORATORIES, INC.,
Defendants-Appellees,

and

DOES 2-20,
Defendants.

2010-1401

Appeal from the United States District Court for the Central District of California in case no. 08-CV-1349, Senior Judge Mariana R. Pfaelzer.

Decided: April 29, 2011

ROBERT D. FISH, Fish & Associates, P.C., of Irvine, California, argued for plaintiff-appellant.

BRIAN C. CANNON, Quinn Emanuel Urquhart & Sullivan, LLP, of Redwood Shore, California, argued for defendants-appellees. With him on the brief were KEVIN P.B. JOHNSON; and RORY S. MILLER and KRISTIN J. MADIGAN, of Los Angeles, California.

Before GAJARSA, LINN, and MOORE, *Circuit Judges*.

GAJARSA, *Circuit Judge*.

This is an appeal from a patent infringement action involving a genetic test for Type I hereditary hemochromatosis. Billups-Rothenberg, Inc. ("Billups") sued Associated Regional and University Pathologists, Inc. ("ARUP") and Bio-Rad Laboratories, Inc. ("Bio-Rad") alleging infringement of U.S. Patent Nos. 5,674,681 ("'681 patent") and 6,355,425 ("'425 patent") (collectively, "patents-in-suit"). The parties filed cross-motions for summary judgment. The district court denied Billups's motion for summary judgment of infringement and granted ARUP and Bio-Rad's motion for invalidity. In its order, the district court concluded that (1) the asserted claims of the '681 patent were invalid for lack of written description and (2) the asserted claims of the '425 patent were invalid as anticipated because U.S. Patent No. 6,025,130 ("'130 patent") disclosed the claimed genetic test for a specific mutation implicated in Type I hereditary hemochromatosis. Order at 2, *Billups-Rothenberg, Inc. v. Associated Reg'l & Univ. Pathologists, Inc.*, No. 08-CV-21349 (C.D. Cal. May 26, 2010), ECF No. 248 ("*Summ. J. Order*"). Because the district court properly granted summary judgment on both asserted patents, we affirm.

BACKGROUND

Deoxyribonucleic acid ("DNA") is the chemical name for the genetic material that forms the basis of heredity in

humans. DNA is composed of sequences of four nucleotides: adenine, thymine, guanine, and cytosine (abbreviated A, T, G, and C, respectively) arranged in functional units known as genes. Each gene codes for a sequence of amino acids that make up peptides and proteins. The relationship between a nucleotide sequence and the corresponding amino acid sequence is known as the genetic code. Mutations that alter a sequence of nucleotides may change the corresponding amino acid sequence, which in turn may affect the structure or function of the protein encoded by the gene.

DNA is packaged into structures known as chromosomes. In somatic cells, humans have one pair of sex chromosomes and twenty-two pairs of autosomal chromosomes, which are numbered according to size from the largest to the smallest. One chromosome per pair is inherited from each parent. Each chromosome is composed of two arms, known as the short arm and long arm.

The patents-in-suit describe genetic tests for Type I hereditary hemochromatosis, an iron disorder characterized by excessive iron absorption by the body. Hereditary hemochromatosis is caused by specific mutations in a gene involved in regulating iron absorption. The gene in question, the *H*igh *Fe* ("*HFE*") gene ("Fe" is the chemical symbol for iron), is located on the short arm of chromosome six in humans. The *HFE* gene codes for the HFE protein, also known as the human hemochromatosis protein. When certain mutations occur in the *HFE* gene, the resulting mutated HFE protein results in increased iron absorption from the gut. Hereditary hemochromatosis is an autosomal recessive condition, meaning that a person must inherit one mutated form of the *HFE* gene from each parent to develop the disease. Not everyone with two mutated *HFE* genes becomes clinically ill and, in some cases, inheriting only one mutated gene in combina-

tion with mutations in other genes may lead to some increased iron absorption. The claims of the patents-in-suit are directed to the detection of one or both of two distinct mutations in the *HFE* gene, known as C282Y and S65C. The prior art '130 patent describes three mutations in the *HFE* gene: C282Y, S65C, and H63D.

In 1994, Billups filed the application for the '681 patent, entitled "Methods to Identify Hemochromatosis." Dr. Barry E. Rothenberg, the founder of Billups, was named as the inventor. The '681 patent explains that Type I hereditary hemochromatosis ("hemochromatosis") is a disease caused by a gene linked to the major histocompatibility complex ("MHC"). '681 patent col.17 ll.51-54. The genes associated with the MHC code for a variety of products, many of which defend the body against pathogens. The '681 patent identifies human chromosome six as the location of the gene responsible for hemochromatosis. *Id.* col.17 ll.53-54. The specification of the '681 patent addresses how to detect a mutation:

> A mutation in a nucleic acid sequence can be detected by various methods to analyze nucleic acids such as by nucleic acid sequencing, polymerase chain reaction or hybridization. Such methods are well known to those in the art (see, for example, Sambrook et al, supra, 1989; Hames and Higgins *Nucleic Acid Hybridisation: a practical approach* (IRL Press, New York, 1985), both of which are incorporated herein by reference).

Id. col.23 ll.26-33.

Although some of the '681 patent's claims also cover testing for hemochromatosis by detecting defective proteins in a patient's blood, only claims covering the genetic test for what is now known as the C282Y mutation are

asserted in this case. Claim 2, which is representative of the asserted claims, reads:

> 2. A method to identify an individual having or predisposed to having hemochromatosis, comprising the steps of:
>
> a) providing from the individual a sample containing a gene encoding a nonclassical MHC class I heavy chain
>
> and
>
> b) detecting a mutation in said gene, which mutation results in the reduced ability of said heavy chain to associate with said ß$_2$ microglobulin, wherein the presence of said mutation identifies said individual as having or predisposed to having hemochromatosis.

Id. col.31 ll.19-24.

Although Billups claimed methods of detecting mutations responsible for hemochromatosis in the '681 patent, it had not yet identified any disease-causing mutations. In August of 1995, Dr. Rothenberg employed Dr. Ritsuko Sawada-Hirai to help him identify the mutations responsible for hemochromatosis. They were unable to isolate the hemochromatosis gene or any mutations of the gene.

Others, however, had more success. In 1996, Dr. John N. Feder and a group of scientists unaffiliated with Billups isolated and sequenced the hemochromatosis gene and published their results. John N. Feder et. al., *A Novel MHC Class I-like Gene is Mutated in Patients with Hereditary Haemochromatosis*, 13(4) Nature Genetics 399 (1996). This group of researchers specifically noted that "further refinement of the location of this gene has been difficult." *Id.* at 399. This research resulted in numerous U.S. and foreign patents, including the '130 patent, enti-

tled "Hereditary Hemochromatosis Gene." The '130 patent discloses the exact genetic sequences for the three mutations at issue in this case: C282Y, H63D, and S65C. *See, e.g.*, fig.4A (genetic code for the H63D and S65C mutations identified as 24d2 and 24d7, respectively); fig.4C (genetic code for the C282Y mutation identified as 24d1).

Fig. 4A

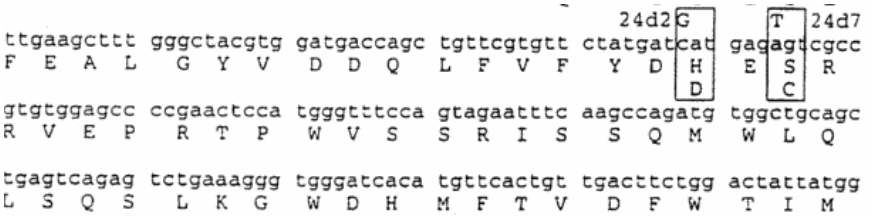
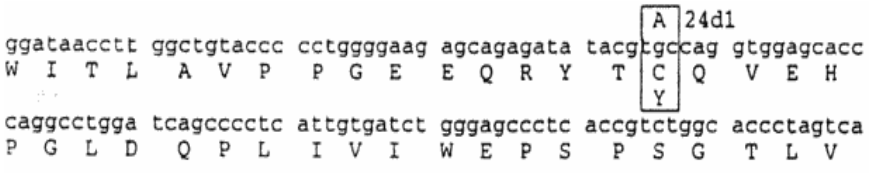


Fig. 4C



Also, the '130 patent describes genetic tests for hemochromatosis utilizing the mutations and sequence variants identified within the patent. *Id.* col.23 ll.10-67. Bio-Rad is the assignee of the '130 patent and licenses it to ARUP, a laboratory at the University of Utah that provides genetic testing services.

Dr. Feder and his team published their discovery while ARUP was continuing to search for the hemochromatosis gene and its mutations. In October 1998, a medical director at ARUP published a paper describing how the genetic probes for the H63D mutation also accidentally identified the nucleotide sequence A193T, which corresponds to the S65C mutation. ARUP developed this

assay into the genetic test presently accused of infringing the patents-in-suit. The assay detected the C282Y, H63D, and S65C mutations in samples from patients.

At the same time, the Billups researchers also used the genetic sequences discovered by Dr. Feder and his team to refine their own experiments. On March 26, 1999, Dr. Rothenberg, Dr. Sawada-Hirai, and collaborator Dr. James Barton filed the application that matured into the '425 patent. The '425 patent claims a method for diagnosing an iron disorder by testing for genetic mutations including S65C.

Claim 1 of the '425 patent appears below:

> 1. A method of diagnosing an iron disorder or a genetic susceptibility to developing said disorder in a mammal, comprising determining the presence of a mutation in exon 2 of an HFE nucleic acid in a biological sample from said mammal, wherein said mutation is not a C→G substitution at nucleotide 187 of SEQ ID NO: 1 and wherein the presence of said mutation is indicative of said disorder or a genetic susceptibility to developing said disorder.

'425 patent col.59 ll.19-26.

Table 1 of the '425 patent labels a genetic sequence identical to the genetic sequence in Figure 4A of the '130 patent as "S65C." *Cf.* '425 patent col.1-2 Table 1 ("gag*agt*cgcc"); '130 patent fig.4A ("gag*agt*cgcc"). Additionally, the '425 patent explains that two of the twenty hemochromatosis patients had the S65C mutation. '425 patent col.31 ll.20-37 table 6, col.32 l.8 ("Probands 3 and 4 had a S65C mutation.") The inventors of the '425 patent concluded that the S65C mutation could be used to diagnose hemochromatosis. *Id.* col.32 ll.8-13.

In 2009, Billups sued ARUP and Bio-Rad for infringement of the patents-in-suit. Billups amended its complaint and alleged that ARUP and Bio-Rad infringe the patents-in-suit by "providing and/or using diagnostic assays or kits for detecting hemochromatosis" associated with one or both of the C282Y and S65C mutations. Am. Compl. ¶ 14. After completion of discovery, a *Markman* hearing, and claim construction by the court, the parties filed cross-motions for summary judgment. The district court granted summary judgment of invalidity for lack of a written description to ARUP and Bio-Rad. The district court found it undisputed that: "The DNA sequence of the hemochromatosis gene and/or sequence of the C282Y mutation were not expressly specified in the '681 patent." *Summ. J. Order* 3. Further, the district court noted that it is "undisputed by the parties that no species of the genus of DNA mutations, the presence of which would identify an individual as having or being predisposed to having hemochromatosis, were disclosed in the '681 patent specification." *Id.* at 6. The district court further stated that "[d]escribing the structure of the resulting protein is not the same as describing the structure of the DNA and its mutations. The invention claimed in the '681 patent is a method to test for a DNA mutation, not a test for a defective protein." *Id.* Additionally, the district court explained that the "patentee has merely directed the person of ordinary skill in the art to a general location of a mutation on a chromosome and suggested that the mutation may be found in that vicinity." *Id.* at 8. The district court held the asserted claims of the '681 patent invalid for lack of written description. The district court concluded that ARUP and Bio-Rad's enablement arguments were "persuasive," but declined to rule on them in light of its ruling that the claims failed the written description requirement. *Id.* at 9.

The district court also granted summary judgment of invalidity of the '425 patent. First, it held that Bio-Rad's '130 patent was prior art under 35 U.S.C. § 102(e) because it was filed on May 23, 1996, which is before the March 1999 filing date of the '425 patent. *Id.* at 3-4, 10. Then, the district court determined that the asserted claims of the '425 patent are anticipated because they claim "the same genetic test for S65C as is disclosed in the '130 patent." *Id.* at 10. The district court entered final judgment in favor of ARUP and Bio-Rad dismissing the case. This court has jurisdiction over Billups's timely filed appeal pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

This court reviews an order of summary judgment *de novo*. *See, e.g.*, *Amgen, lnc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1339 (Fed. Cir. 2003). Summary judgment must be granted when, drawing all reasonable inferences in favor of the non-movant, there is no genuine issue as to any material fact. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986); Fed. R. Civ. P. 56(c). We first examine whether the asserted claims of the '681 patent are invalid for lack of written description. Then, we determine whether the asserted claims of the '425 patent are invalid as anticipated.

I

Written description is a statutory requirement set forth in 35 U.S.C. § 112. The written description requirement requires the inventor to disclose the claimed invention so as to "allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (internal quotations omitted). "Requiring a written description of the invention limits patent protection to those who actually per-

form the difficult work of 'invention'—that is, conceive of and complete the final invention." *Id.* The written description requirement exists to ensure that inventors do not "attempt to preempt the future before it has arrived." *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993). In *Fiers*, a party's priority application failed to provide an adequate written description as it purported to cover all DNAs coding for a specific protein but did not describe the DNA. The party only provided a generic reference that the DNA could be obtained by reverse transcription and this court held that "[c]laiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement." *Id.*

The "level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Ariad*, 598 F.3d at 1351 (citing *Capon v. Eshhar*, 418 F.3d 1349, 1357-58 (Fed. Cir. 2005)). "[A]n adequate description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67 (Fed. Cir. 1997) (internal quotations omitted). Complementary DNA ("cDNA") is a form of DNA that only contains exons, stretches of DNA that code for genes. In *Regents*, a claim to a cDNA invention was held invalid as lacking written description because such a claim "requires a specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." *Id.* at 1569.

Billups claims that its disclosure of the mutation's general location somewhere "within less than a 300 base pair region of a defined exon of a well studied multi-gene family," combined with the knowledge that existed at the

time of filing the '681 patent, established that Dr. Rothenberg possessed the claimed invention. Appellant's Br. 9. The '681 patent claims a test for mutations, yet it is undisputed that the specification and originally filed claims of the '681 patent disclose neither the hemochromatosis gene sequence nor any specific mutations within that gene. Although the '681 patent states that the hemochromatosis mutations are in a gene encoding the α3 domain of a nonclassical MHC class I heavy chain located on the short arm of chromosome six, that does not disclose the exact location or sequence of the mutation. '681 patent col.32 ll.13-14. Billups did not possess a genetic mutation useful for diagnosing hemochromatosis when it filed its patent application in December of 1994. The '681 patent merely represents Billups's research plan. *See Ariad*, 598 F.3d at 1351.

Billups maintains that based on knowledge outside the patent, including the subsequent discovery of C282Y, the '681 patent adequately described the envisioned, but then unknown, mutations. Given the lack of knowledge of sequences for the hemochromatosis gene and its mutations in the field, the limited extent and content of the prior art, and the immaturity and unpredictability of the science when the '681 patent was filed, Billups cannot satisfy the written description requirement merely through references to later-acquired knowledge. This case is like *Regents* and *Fiers*, in which the DNA sequences at issue were unknown in the art. *Regents*, 119 F.3d at 1567-69; *Fiers*, 984 F.2d at 1171.

The '681 patent claims methods covering the identification of a genus of unknown genetic mutations. '681 patent col.31 ll.19-24. A claim encompassing two or more disclosed embodiments within its scope is a genus claim. For genus claims, "an adequate written description of a claimed genus requires more than a generic statement of

an invention's boundaries." *Ariad*, 598 F.3d at 1349 (citing *Regents*, 119 F.3d at 1568). Under *Ariad*, a patent must set forth "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus." *Id.* at 1350. The '681 patent does not identify even a single species that satisfies the claims. In this case, the eventual discovery of only one species—the C282Y mutation—within the claimed genus does not constitute adequate written description of that genus.

Ariad also explained that "[f]unctional claim language can meet the written description requirement when the art has established a correlation between structure and function." *Id.* Billups maintains that the '681 patent satisfies the written description requirement because it contains functional claim language. Billups contends that the '681 patent taught structure, i.e., that hemochromatosis has a genetic basis, and function, namely, its adverse effect upon the binding of $ß_2$ microglobulin with a non-classical MHC class I heavy chain. Specifically, Billups argues that the '681 patent's correlation of function with the general location of the C282Y mutation, combined with the knowledge of a person of ordinary skill in the art in the field at the time of filing, satisfied the written description requirement by localizing the mutation to a 300 base pair region.

The district court, however, found that the art did not establish a correlation between structure and function because the "[p]atentee's general location disclosure is too imprecise to constitute structural features necessary to meet the written description requirement." *Summ. J. Order* 6-9. As explained in the district court's order, the "specification for the '681 patent contains only functional, not structural, characteristics of the predicted mutations." *Id.* at 7. The district court properly granted summary

judgment to Appellees that there is no genuine issue of material fact that the asserted claims of the '681 patent are invalid for lack of written description requirement.

Finally, Billups argues that the district court erred in failing to rule upon whether the '681 patent satisfied the enablement requirement of 35 U.S.C. § 112. Because the district court properly granted summary judgment that the '681 patent does not satisfy the written description requirement, it was not erroneous for it to decline to rule upon whether the '681 patent satisfied the enablement requirement of 35 U.S.C. § 112.

II

A patent claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference. 35 U.S.C. § 102. The asserted claims of the '425 patent are invalid because they are anticipated by the '130 patent. The '130 patent was filed nearly three years before the '425 patent and is prior art under § 102(e). The district court correctly ruled that the '130 patent discloses use of the S65C mutation as a "HH [(hereditary hemochromatosis)] diagnostic," and, thus, Billups was not the first to disclose diagnosis of hemochromatosis using the S65C mutation. *Summ. J. Order* 11.

The '130 patent discloses the genetic sequence of the S65C mutation and describes a genetic assay for detecting one or more of the C282Y, H63D, and S65C mutations. In an example entitled "HH Diagnostic: Other Nucleotide Based Assays," the specification of the '130 patent states that

> any combination of such techniques [for conducting a genetic assay] can be used in accordance with the invention for the design of a diagnostic

> device and method for the screening of samples of DNA or RNA for HH gene mutations in accordance with the invention, such as the mutations and sequence variants identified herein (24d1, 24d2, and 24d7).

'130 patent col.38 l.64-col.39 l.8. The variants correspond to the C282Y, H63D, and S65C mutations, respectively.

Billups contests whether the '130 patent discloses the subject of the '425 patent, namely, the diagnosis of an iron disorder using the S65C mutation. It is undisputed that the S65C mutation falls within claim 1 of the '425 patent. Billups argues that the '425 patent claims a genetic predisposition to an iron disorder or the diagnosis of such a predisposition, but the '130 patent merely correlates the S65C mutation and hemochromatosis. Billups interprets the '130 patent as concluding that the S65C mutation was only a clinically insignificant polymorphism unrelated to disease state. Thus, Billups contends that the '130 patent did not teach using the S65C mutation to diagnose hemochromatosis.

Billups's argument is based on the portion of the '130 patent stating:

> In Table 4, the 24d7(T) allele was observed in only one chromosome present in the patient sample (HC43) (0.4%) and present in four chromosomes from the unaffected individuals (3%). The presence of the 24d7(T) allele shows no increase in risk of acquiring HH and thus may only be a polymorphic variant within the population.

Id. col.19 ll.22-27.

Despite the inventors' uncertainty regarding the utility of the S65C mutation because of their small sample size, the '130 patent describes two genetic tests for hemo-

chromatosis that involve detection of the S65C mutation as an input for the diagnosis of hemochromatosis. The patent describes one genetic test as "HH diagnostic," meaning that it could be used in the diagnosis of hemochromatosis. *Id.* col.38 l.65-col.39 l.40. The patent also describes a test kit for hemochromatosis mutations, including S65C. *Id.* col.38 ll.49-52.

Although the '130 patent discounts the utility of the S65C mutation in diagnosing hemochromatosis, we have held that a "reference is no less anticipatory if, after disclosing the invention, the reference then disparages it." *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998). Indeed, in *Celeritas*, this court explained that "whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis." *Id.* (quoting *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 772 (Fed. Cir. 1983)). In *Celeritas*, this court considered prior art stating that "de-emphasis would cause severe inter-symbol interference in a single-carrier data signal; it *may* be feasible only for multicarrier signals." *Id.* (emphasis added). This court held that the disclosure was sufficient to anticipate and invalidate the claims of the asserted patent, as "[t]he fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed. The modem in the article is not disclosed to be inoperative." *ld.*

Like the prior art reference in *Celeritas*, the '130 patent discloses using the S65C mutation when diagnosing hemochromatosis, but qualifies that disclosure with the observation that the mutation "*may* only be a polymorphic variant." '130 patent col.19 ll.25-27 (emphasis added). In both cases, the prior art questioned the utility of an application of the disclosed invention but, nevertheless, disclosed the invention. Likewise, the *Kalman* case states

that "it is only necessary that the claims under attack, as construed by the court, read on something disclosed in the reference." 713 F.2d at 772, *overruled in part on other grounds*, *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1125 (Fed. Cir. 1985) (en banc) (internal quotations omitted). In the present case, the district court correctly recognized that the '130 patent discloses a diagnostic test for hemochromatosis that included identification of the S65C mutation, and, therefore, anticipated the '425 patent's claims.

At oral argument, Billups conceded that it waived its argument that the '130 patent cannot be used to anticipate because the relevant teachings were not enabled. Oral Arg. at 25:23-25:50; 29:23-29:56, *available at* http://www.cafc.uscourts.gov/oral-argument-recordings/all/billups.html. Even if this argument had not been waived, the district court presumes the enablement of the material in a prior art patent, and Billups failed to present evidence of nonenablement that the district court found persuasive. The '130 patent may be used to anticipate the '425 patent. Even though the inventors of the '425 patent performed experiments revealing greater diagnostic utility of the S65C mutation than initially suspected, the use of the S65C mutation as a diagnostic tool was already contemplated by the '130 patent. Accordingly, there is no genuine issue of material fact that the asserted claims of the '425 patent are invalid because they are anticipated by the '130 patent.

CONCLUSION

Because the district court properly granted summary judgment to Appellees that the asserted claims of the '681 patent are invalid for lack of written description and the asserted claims of the '425 patent are invalid as anticipated, we affirm the judgment of the district court.

AFFIRMED

COSTS

No costs.