

# United States Court of Appeals for the Federal Circuit

2006-1334, -1452

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA,  
ABBOTT MOLECULAR, INC., and ABBOTT LABORATORIES, INC.,

Plaintiffs-Appellants,

v.

DAKOCYTOMATION CALIFORNIA, INC.,

Defendant-Appellee.

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2007-1202

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA,  
ABBOTT MOLECULAR, INC., and ABBOTT LABORATORIES, INC.,

Plaintiffs-Appellants,

v.

DAKO A/S,  
and DAKO NORTH AMERICA, INC.,

Defendants-Appellees.

James F. Hurst, Winston & Strawn, LLP, of Chicago, Illinois, argued for plaintiffs-appellants. On the briefs were Lynn H. Pasahow, Heather N. Mewes, Carolyn C. Chang, and C.J. Alice Chuang, Fenwick & West, LLP, of Mountain View, California. Of counsel was Virginia K. DeMarchi.

Thomas H. Jenkins, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., of Washington, DC, argued for all defendants-appellees. With him on the briefs were Anthony C. Tridico, of Washington, DC, and Tina E. Hulse and David C. Hoffman, of Palo Alto, California. On the brief for defendant-appellee Dakocytomation California, Inc. was Richard J. Smith, of Palo Alto, California.

Appealed from: United States District Court for the Northern District of California

Judge Marilyn H. Patel

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Defendants-Appellees.

Appeal from the United States District Court for the Northern District of California in Case No. 05-CV-03955, Judge Marilyn Hall Patel.

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DECIDED: February 28, 2008

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Before MAYER, LOURIE, and PROST, Circuit Judges.

Opinion for the court filed by Circuit Judge LOURIE. Opinion dissenting in part filed by Circuit Judge PROST.

LOURIE, Circuit Judge.

The Regents of the University of California and Abbott Molecular Inc. and Abbott Laboratories Inc. (collectively referred to as “appellants”) appeal from two decisions of the United States District Court for the Northern District of California. Appellants first appeal the district court’s denial of their motion for a preliminary injunction enjoining Dako A/S and Dako North American, Inc. (“Dako”) from manufacturing and selling its HER2 FISH pharmDX™ kit (“HER2 kit”), which appellants allege infringe the patents in suit, *viz.*, U.S. Patents 5,447,841 (“the ’841 patent”) and 6,596,479 (“the ’479 patent”). Appellants also filed an interlocutory appeal from the district court’s decision granting in part summary judgment of noninfringement of these patents. Because we conclude that the district court correctly construed the term “heterogeneous mixture of labeled unique sequence nucleic acid fragments,” erred in its construction of “morphologically identifiable cell nucleus,” and erred by concluding that appellants were barred by the doctrine of prosecution history estoppel, we affirm in part, reverse in part, and remand for further proceedings.

## BACKGROUND

### A. Background on Technology

The cells of living organisms contain chromosomes—structures in the cell nucleus that are composed in part of deoxyribonucleic acid (“DNA”). DNA is a complex molecule that encodes the genetic information of an organism. In order for a cell to replicate and divide, it undergoes a process known as mitosis. There are two main phases in the cell-division cycle—metaphase and interphase. During metaphase, the chromosomes are condensed and are thus visible with a microscope. At this stage of

mitosis, the condensed chromosomes align in the middle of the cell before dividing into two daughter cells. That phase is relatively short-lived, as the rest of the cycle is spent in interphase. During interphase, the chromosomes are not visible with a microscope because they are not condensed and are spread throughout the nucleus.

The inventions claimed in the patents in suit are directed to improved “methods for identifying and classifying chromosomes” in order to detect chromosomal abnormalities. ’841 patent col.1 ll.21-22.<sup>1</sup> Such abnormalities “are associated with genetic disorders, degenerative diseases, and exposure [sic] to agents known to cause degenerative diseases,” such as cancer. Id. col.1 ll.23-26. There are three general types of chromosomal abnormalities, viz., extra or missing individual chromosomes, extra or missing portions of a chromosome, or chromosomal rearrangements. Id. col.1 ll.34-36. While a normal human cell contains twenty-three pairs of chromosomes, the genetic disorder known as Down syndrome, for example, is caused by an extra copy of chromosome 21. Id. col.1 ll.45-46.

Several problems existed in the prior art with respect to screening chromosomes. First, procedures in the prior art were limited to and required that chromosomes be in the metaphase phase of the cell cycle. Those procedures required use of metaphase chromosomes because it was not “possible to visualize nonmetaphase, or interphase chromosomes due to their dispersed condition in the cell nucleus.” Id. col.2 ll.19-23. The procedures used cytological techniques to stain the chromosomes, thereby revealing “a longitudinal segmentation into entities generally referred to as bands.” Id.

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<sup>1</sup> The ’479 patent is a divisional of the ’841 patent, and has a specification that is nearly identical to that of the ’841 patent. For ease of reference, throughout the opinion we will cite the ’841 patent when referencing the common specification.

col.2 II.25-27. Banding analysis, however, required “cell culturing and preparation of high [q]uality metaphase spreads, which is extremely difficult and time consuming, and almost impossible for tumor cells.” Id. col.2 II.36-39.

Second, other prior art techniques, which used probes comprised of DNA and RNA fragments for gene mapping, were limited by the nonspecificity of that technique. Those probes “comprise labeled fragments of single stranded or double stranded DNA or RNA which are hybridized to complementary sites on chromosomal DNA.” Id. col.2 II.57-60. The hybridization process of the labeled probes to the target chromosomal DNA requires the denaturation, or the unraveling, of the double-stranded nucleic acids by heating or some other means. Id. col.3 II.4-17. That process then requires several additional steps. A problem associated with that technique, however, was the nonspecificity of the staining reagents due to repetitive nucleotide sequences that were present throughout the chromosomes. Id. col.4 II.47-52. Nucleotide sequences are generally divided into three different categories based on their frequency: highly repetitive (or satellite DNA), which is located in the centromeric region of the chromosome; middle-repetitive, which is generally interspersed among unique sequences; or unique. Id. col.4 II.27-30. The presence of repetitive sequences “greatly reduces the degree of chromosome-specificity of the staining reagents of the invention, particularly in genomes containing a significant fraction of repetitive sequences, such as the human genome.” Id. col.8 II.40-44. Labeled probes would not only hybridize with the target chromosomal DNA, but with repetitive sequences as well, thereby producing unacceptable false-positive results.

In light of those problems, the patentees sought to employ a staining technique that “open[ed] up the possibility of rapid and highly sensitive detection of chromosomal abnormalities in both metaphase and interphase cells using standard clinical and laboratory equipment.” Id. col.5 ll.29-33. To increase the specificity of the staining reagents, the patents at issue state that it is “desirable to disable the hybridization capacity of repetitive sequences.” Id. col.4 ll.47-48. The specification discloses three ways to disable the hybridization capacity of the repetitive sequences, consisting of blocking, selective removal, and screening of repetitive sequences. The '841 patent claims are directed to blocking the repetitive sequences. Claim 1 of the '841 patent reads as follows:

1. A method of staining target chromosomal DNA comprising:

(a) providing 1) labeled nucleic acid that comprises fragments which are substantially complementary to nucleic acid segments within the chromosomal DNA for which detection is desired, and 2) blocking nucleic acid that comprises fragments which are substantially complementary to repetitive segments in the labeled nucleic acid; and

(b) employing said labeled nucleic acid, blocking nucleic acid, and chromosomal DNA in in situ hybridization so that labeled repetitive segments are substantially blocked from binding to the chromosomal DNA, while hybridization of unique segments within the labeled nucleic acid to the chromosomal DNA is allowed, wherein blocking of the labeled repetitive segments is sufficient to permit detection of hybridized labeled nucleic acid containing unique segments, and wherein the chromosomal DNA is present in a morphologically identifiable chromosome or cell nucleus during the in situ hybridization.

'841 patent, claim 1 (emphases added). During prosecution of the '841 patent, the patentees indicated that the claims of the patent were limited to the blocking embodiment. They further indicated that claims to the other major embodiment of

disabling the hybridization capacity, i.e., by removal of the repetitive sequences, would be pursued in another patent application. That application resulted in the '479 patent.

Claim 1 of the '479 patent reads as follows:

1. A method of staining target interphase chromosomal DNA to detect an extra or missing portion or portions of a chromosome, or a translocation or an inversion of a portion or portions of a chromosome, the method comprising:

(a) providing a heterogeneous mixture of labeled unique sequence nucleic acid fragments which are substantially complementary to nucleic acid segments within the interphase chromosomal DNA for which detection is desired and are designed to allow detection of an extra or missing portion or portions of a chromosome, or a translocation or an inversion of a portion or portions of a chromosome;

(b) employing the heterogeneous mixture and interphase chromosomal DNA in *in situ* hybridization to permit detection of labeled nucleic acid fragments which are hybridized to interphase chromosomal DNA, wherein the chromosomal DNA is present in a morphologically identifiable cell nucleus during the *in situ* hybridization; and

(c) detecting the labeled nucleic acid fragments which are hybridized to the interphase chromosomal DNA to determine whether an extra or missing portion or portions of a chromosome, or a translocation or an inversion of a portion or portions of a chromosome is present in the target interphase chromosomal DNA.

'479 patent claim 1 (emphases added). The '479 patent does not refer to the blocking method. Instead, the claimed invention of the '479 patent employs compositions that are comprised of "a heterogeneous mixture of labeled unique sequence nucleic acid fragments" that excludes repetitive sequences. Thus, the invention of the '479 patent employs the method of removing or screening repetitive sequences from the heterogeneous mixture in order to disable the hybridization capacity of repetitive sequences—in contrast to using blocking nucleic acid, as claimed in the '841 patent.

B. Procedural Background

On September 29, 2005, appellants, who are the owner and exclusive licensee of the patents in suit, filed a complaint for patent infringement against Dako. On October 14, 2005, appellants filed a motion for preliminary injunction seeking to prohibit Dako from manufacturing and selling its HER2 kit. The court denied appellants' motion on March 10, 2006. In denying the motion, the court concluded that appellants failed to show a likelihood of success on the merits of their infringement claim under the '479 patent based on, inter alia, its claim construction of two claim limitations, viz., "morphologically identifiable chromosome or cell nucleus" and "heterogeneous mixture of labeled unique sequence nucleic acid fragments." The court also based its conclusion on appellants' failure to show a likelihood of success that the accused product met the "blocking nucleic acid" limitation of the '841 patent under the doctrine of equivalents.

On March 30, 2006, appellants appealed the district court's denial of the preliminary injunction. While that appeal was pending, the district court issued another order on May 17, 2006, amending the basis for its denial of the preliminary injunction. Specifically, the district court amended its basis for rejecting appellants' proposed construction of the term "heterogeneous mixture of labeled unique sequence nucleic acid fragments." In the original order denying the preliminary injunction, the district court rejected appellants' proposed construction of that term, which only appears in the '479 patent, based on its conclusion that the '841 patent is prior art to the '479 patent, and that adopting appellants' proposed construction would likely render the '479 patent invalid. The court amended "its previous order to the extent it improperly cite[d] 35

U.S.C. § 102 as the basis for questioning the validity of the claims of the '479 patent" in light of the '841 patent, and instead stated that the '479 patent would likely be rendered invalid under the doctrine of nonstatutory (obviousness) double patenting. Appellants then appealed from the court's amended order, and both preliminary injunction appeals were consolidated for briefing and oral argument.

While the appeals were pending, Dako moved for summary judgment of noninfringement. Prior to ruling on that motion, the district court held a Markman hearing and construed certain claim limitations. On July 31, 2006, the court granted summary judgment of noninfringement of the '479 patent as to all of the accused products based on its construction of the "heterogeneous mixture" limitation. The court further granted summary judgment of noninfringement on the '841 patent as to two of Dako's products, viz., the HER2 kit and TOP2A kit, upon concluding that appellants were barred from asserting infringement of the "blocking nucleic acid" limitation under the doctrine of equivalents. The court also denied summary judgment on the '841 patent as to the remaining twenty accused products. The court did not address whether Dako's products met the "morphologically identifiable" limitation—a claim limitation that was at issue in the preliminary injunction motion.

The parties jointly filed a motion to certify for immediate appeal the district court's summary judgment order under 28 U.S.C. § 1292(b) and to stay the proceedings. The district court granted the motion on December 15, 2006, and on February 14, 2007, we granted permission to appeal the interlocutory order. While we have not generally certified motions for interlocutory appeal of claim construction, we determined that it was especially desirable in this case in view of the pendency of the related appeal on

the denial of the preliminary injunction based on some of the same issues. At oral argument, the parties agreed that the preliminary injunction appeals and the summary judgment appeal should be considered together in light of the overlapping issues that are before us. We have jurisdiction pursuant to 28 U.S.C. § 1292(c)(1).

## DISCUSSION

### A. Standard of Review

Appellants raise three issues in their combined appeal from the preliminary injunction and summary judgment orders. Two issues concern claim construction and the other concerns prosecution history estoppel. We review claim construction, which is an issue of law, Markman v. Westview Instruments, Inc., 52 F.3d 967, 970-71 (Fed. Cir. 1995) (en banc), de novo. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). Whether the district court erred in its application of prosecution history estoppel to limit the effect of the doctrine of equivalents is also a question of law that is reviewed de novo. Pharmacia & Upjohn Co. v. Mylan Pharms., Inc., 170 F.3d 1373, 1376 (Fed. Cir. 1999).

### B. Issues Presented in the Summary Judgment Appeal<sup>2</sup>

#### 1. Construction of “heterogeneous mixture of labeled unique sequence nucleic acid fragments”

In both the preliminary injunction and summary judgment appeals, appellants argue that the district court erred in its construction of the claim limitation “heterogeneous mixture of labeled unique sequence nucleic acid fragments,” a limitation

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<sup>2</sup> We first address the issues raised in the summary judgment appeal, as our decision concerning the construction of “heterogeneous mixture” in that case has a dispositive impact on the preliminary injunction appeal.

that is required by every claim of the '479 patent. The court construed that language to mean "heterogeneous mixture of labeled nucleic acid fragments that includes only unique sequence fragments," whereas Dako's kits contain repetitive sequences. Appellants assert that the court erred by interpreting that language to mean that the heterogeneous mixture excludes repetitive sequences. They assert that that construction is contrary to the fact that the dependent claims of the patent clearly require repetitive sequences. Appellants further argue that the district court erred by relying on the prosecution history in support of its construction. According to appellants, the term "unique sequence" was not added to the claim to limit the scope of the heterogeneous mixture, as the court concluded. Rather, it was added to clarify that the invention related to the detection of unique sequences, as opposed to the detection of repetitive sequences as taught in the prior art.

In response, Dako argues that the intrinsic evidence supports the district court's construction. According to Dako, the claim language supports a construction that excludes repetitive sequences, notwithstanding the dependent claims, because the specification supports that construction in statements and embodiments and in light of the prosecution history of the '479 patent. In addition, Dako argues that the doctrine of claim differentiation is not an absolute rule. Where construction of an independent claim leads to a clear conclusion inconsistent with a dependent claim, the doctrine of claim differentiation must yield.

In its initial order denying preliminary injunctive relief, the court concluded that the heterogeneous mixture excludes repetitive sequences in light of the '841 patent, which the court characterized as prior art to the '479 patent. The court reasoned that

appellants' construction, which contemplates the use of both unique and repetitive sequences, raised "serious concerns about the [appellants'] ability to simultaneously preserve validity and establish infringement with respect to the claim of the '479 patent."

Regents of Univ. of Cal. v. DakoCytomation Cal., Inc., No. 05-CV-03955, 2006 WL 618769, at \*9 (N.D. Cal. Mar. 10 2006). Thus, the court rejected appellants' proposed construction upon concluding that it would likely render the patent invalid under 35 U.S.C. § 102(b). The court's reasoning, however, was erroneous because the '479 patent is a division of the '841 patent and claims the priority of the filing date of the '841 patent. See 35 U.S.C. § 120. As such, the court erred in characterizing the '841 patent as prior art, and thus erred in concluding that the '841 patent would likely render the '479 patent invalid if appellants' construction had been adopted.

After realizing its error, the district court issued an amended preliminary injunction order, relying on a new basis for rejecting appellants' proposed construction. The court reasoned that that construction would likely render the '479 patent invalid based on nonstatutory (obviousness) double patenting in view of the '841 patent. Appellants, however, had previously filed a terminal disclaimer, which cures such a double patenting rejection. Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1378 (Fed. Cir. 2003). Thus, the court erred by rejecting appellants' construction on that basis as well.

Although the district court erred in its reasoning as set forth above, we nonetheless will affirm the court's construction of the heterogeneous mixture limitation. The court correctly evaluated the prosecution history and determined the proper claim construction. We also agree with the court's conclusion set forth in its summary

judgment decision that the patentees disclaimed embodiments that include repetitive sequences during the prosecution of the '479 patent. Thus, the district court was correct in concluding that the accused products, which employ a mixture that includes repetitive sequences, do not infringe the '479 patent.

It is a truism that the claims of a patent define the invention that is claimed, but “the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be.” Phillips v. AWH Corp., 415 F.3d 1303, 1317 (Fed. Cir. 2005) (en banc).

The prosecution history in the present case sheds decisive light on the scope of the disputed claim term. As originally filed, the divisional application that resulted in the '479 patent included a single claim. That claim, claim 17, read:

17. A method of staining chromosomal DNA of a particular chromosome type or portion thereof, or a particular group of chromosome types, the method comprising the steps of:

providing a heterogeneous mixture of labeled nucleic acid fragments, substantial portions of each labeled nucleic acid fragment in the heterogeneous mixture having base sequences substantially complementary to base sequences of the chromosomal DNA; and

reacting the heterogeneous mixture with the chromosomal DNA by *in situ* hybridization.

Supp. J.A. 6592. Notably, the original claim did not include the phrase “unique sequence.”

In April 1996, the examiner issued three separate rejections, including an enablement rejection under § 112, first paragraph; an indefiniteness rejection under

§ 112, second paragraph; and an anticipation rejection in view of three prior art references, viz., Landegent et al., Montgomery et al., and Cannizzaro et al. To overcome those rejections, the patentees canceled claim 17 and submitted a new independent claim, claim 18, as well as several dependent claims. Claim 18 read:

18. A method of staining target interphase chromosomal DNA to detect amplifications, deletion, and rearrangements comprising:

(a) providing a heterogeneous mixture of labeled unique sequence nucleic acid fragments which are substantially complementary to nucleic acid segments within the interphase chromosomal DNA for which detection is desired; and

(b) employing the heterogeneous mixture and interphase chromosomal DNA in *in situ* hybridization to permit detection of labeled nucleic acid fragments which are hybridized to interphase chromosomal DNA, wherein the chromosomal DNA is present in a morphologically identifiable cell nucleus during the *in situ* hybridization.

Supp. J.A. at 6650-51 (emphases added). Thus, the patentees added the “unique sequence” limitation, as well as other limitations regarding interphase chromosomal DNA and a morphologically identifiable cell nucleus. Although the patentees did not expressly state whether the “unique sequence” limitation was added in response to any particular rejection, given the patentees’ arguments accompanying the amendment, as well as previous statements patentees made during the prosecution of the ’841 patent, the term “unique sequence” was clearly added to overcome the enablement rejection.

When issuing the enablement rejection, the examiner stated that “[a]s worded, there is no specificity practice in the actual claim steps that would result in the staining of the target only without so much background that the desired target nucleic acid would be [obscured].” Thus, the examiner recognized that original claim 17 failed to include a limitation directed toward reducing the nonspecific binding of repetitive sequences—a

key problem in the prior art, as disclosed in the specification. The patentees, however, were able to overcome the enablement rejection by limiting the heterogeneous mixture to unique sequences. Indeed, by restricting the heterogeneous mixture to labeled probes of unique sequences, the problem resulting from probes binding to the repetitive sequences would not arise.

That conclusion is supported by the patentees' earlier decision to pursue claims to certain embodiments in the '479 patent, while limiting the '841 patent to the blocking method. When prosecuting the '841 patent, the patentees stated:

The present invention is directed to chromosome-specific staining by *in situ* hybridization. One aspect of the invention involves disabling the hybridization capacity of repeat sequences. In one embodiment, that disabling is performed by selective blocking of the repetitive sequences. All of the newly added claims are directed to this embodiment of the invention.

Previously, the broadest claims had been directed to the generic invention where the repetitive sequences are disabled by any means, the other major embodiment being by removal of the repetitive sequences. Claims to that subject matter, which applicants also believe to be patentable, will be pursued in a separate application.

Supp. J.A. 6124 (emphases added). That separate application became the '479 patent. Notably, the patentees' statements in the prosecution history of the '841 patent indicate two important points, viz., that the disabling of the hybridization capacity of repetitive sequences by blocking was a key aspect of the '841 invention and that claims to embodiments involving the removal of repetitive sequences would be pursued in a separate application. Hence, the addition of "unique sequence" to the heterogeneous mixture limitation, coupled with the patentees' statements during prosecution, evince a clear intent to limit the claims of the '479 patent to those embodiments in which the

repetitive sequences have been excluded from the heterogeneous mixture in order to disable the hybridization capacity of repetitive sequences.

Appellants argue that the addition of the “unique sequence” limitation was not made to overcome the enablement rejection—but instead was added to overcome the anticipation rejection. In particular, appellants contend that the patentees added the “unique sequence” language to the ’479 patent to distinguish the invention from the § 102(b) prior art references. According to appellants, the prior art references used repetitive sequence probes for the detection of repetitive sequences, in contrast to the ’479 invention which used unique sequence probes for the detection of unique sequences. As such, because the addition of “unique sequence” had nothing to do with the issue concerning the nonspecific binding of repetitive sequences—an issue raised by the examiner in connection with the enablement rejection—appellants argue that the patentees did not intend to limit the scope of the heterogeneous mixture by adding “unique sequence” to the claims.

We are not persuaded by appellants’ argument. As a preliminary matter, only two of the three prior art references disclose the use of repetitive sequence probes to detect repetitive sequences. Indeed, appellants acknowledge in their opening brief in support of their summary judgment appeal that the third reference, Cannizzaro et al., “disclosed the use of unique sequence probes.” Thus, the argument that the patentees inserted the “unique sequence” limitation to overcome the anticipation rejection in view of the § 102(b) prior art references is unpersuasive.

Second, the patentees' statements in the Remarks section accompanying the amendment indicate that other language in the amended claim was intended to overcome the anticipation rejection. In particular, the patentees argued:

Claim 17 has been rejected under 35 U.S.C. § 102(b) as being anticipated by any one of Landegent et al, Montgomery et al, or Cannizzaro et al. In view of the cancellation of claim 17 in favor of new claims now of record, it is believed that this rejection in view of the prior art is now moot. The prior art fails to disclose or even suggest the methods of staining target interface [sic] chromosomal DNA to detect amplifications, deletions and rearrangements, as now claimed. Withdrawal of this rejection is thus believed to be in order.

Supp. J.A. 6654 (emphasis added). Thus, based on the plain language of patentees' statements, the patentees overcame the anticipation rejection by clarifying that the claimed method of staining was applied to interphase chromosomal DNA, in contrast to metaphase chromosomal DNA, which was disclosed in the prior art references. Indeed, all three references state that probes for detecting target sequences were used on metaphase chromosomes. See Supp. J.A. at 6618 (Landegent reference stating the procedure was tested and optimized on "mouse satellite sequences in metaphase preparations of a mouse-human hybrid cell line"); id. at 6630 (Montgomery reference stating that "[h]ybridization with metaphase chromosomes in situ has localized these sequences to either the homogeneously staining regions or double-minute chromosomes"); id. at 9646 (Cannizzaro stating that "metaphase [chromosomes were] examined from both subjects") (emphases added). Thus, appellants' contention that the addition of "unique sequence" was added to overcome the anticipation rejection, rather than the enablement rejection, is belied by the patentees' own statements that the

interphase limitation distinguished the invention over the prior art.<sup>3</sup> The “unique sequence” addition was made at least in part to overcome the enablement rejection.

Appellants also argue that the district court’s construction is incorrect in light of certain dependent claims that require inclusion of repetitive sequences. Appellants rely on AK Steel Corp. v. Sollac and Ugine, 344 F.3d 1234, 1242 (Fed. Cir. 2003), for the proposition that “dependent claims are presumed to be of narrower scope than the independent claims from which they depend” under the doctrine of claim differentiation. That argument, however, is likewise unconvincing. Presumptions are rebuttable. We have held that “[w]hile it is true that dependent claims can aid in interpreting the scope of claims from which they depend, they are only an aid to interpretation and are not conclusive.” N. Am. Vaccine, Inc. v. Am. Cyanamid Co., 7 F.3d 1571, 1577 (Fed. Cir. 1993). Indeed, the presumption created by the doctrine of claim differentiation is “not a hard and fast rule and will be overcome by a contrary construction dictated by the written description or prosecution history.” Seachange Int’l, Inc. v. C-COR, Inc., 413 F.3d 1361, 1369 (Fed. Cir. 2005). Here, as discussed above, the prosecution history overcomes the presumption; the correct construction of “heterogeneous mixture” is one that excludes repetitive sequences, notwithstanding the presence of certain dependent claims that do not exclude them.

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<sup>3</sup> We note that in their brief, appellants argue that “the addition of the interphase limitation was not sufficient to overcome the anticipation rejection” with regard to the Landegent reference because that reference “discloses the use of labeled probes to detect repetitive sequences in interphase cells.” Appellants’ Summ. J. Reply Br. at 12 (emphasis added). Our review of that reference, however, reveals that metaphase chromosomes were used in the Landegent experiments and no mention of interphase chromosomes was made. We thus find appellants’ statement to be unsubstantiated and hence unconvincing.

We have considered appellants' additional arguments in support of their position that the heterogeneous mixture does not exclude repetitive sequences, and find no basis for reversing the court's claim construction. Accordingly, having determined that the patentees limited the scope of the heterogeneous mixture to one that only contains unique sequences, the court's claim construction of "heterogeneous mixture containing labeled unique sequence nucleic acid fragments" is affirmed. Thus, the court's grant of summary judgment of noninfringement as to the '479 patent is affirmed.

## 2. Prosecution History Estoppel

The district court also granted summary judgment of noninfringement of the '841 patent as to two accused products, *viz.*, the HER2 kit and the TOP2A kit. In reaching that conclusion, the court addressed the claim limitation "blocking nucleic acid"—a term required by all the claims of the '841 patent. In the district court, the parties stipulated that "blocking nucleic acid" means "fragments of repetitive-sequence-enriched DNA or RNA." Because the HER2 and TOP2A kits do not use human DNA, and instead use synthetic nucleic acids referred to as peptide nucleic acids ("PNA"), the court concluded that those products do not literally infringe the '841 patent. The court then considered whether those products infringe under the doctrine of equivalents. After determining that the patentees narrowed the scope of the "blocking nucleic acid" limitation during prosecution, the court concluded that appellants were barred from asserting that PNAs were an equivalent of a "blocking nucleic acid," and granted summary judgment of noninfringement under the doctrine of equivalents.

Appellants argue that the doctrine of prosecution history estoppel does not apply here because the "nucleic acid" limitation was never narrowed during prosecution. In

the alternative, even if prosecution history estoppel were applicable, appellants argue that the presumption of surrender was overcome because the amendment was merely tangential to the accused equivalent. In response, Dako argues that the court correctly applied the presumption that the patentees surrendered equivalents of the nucleic acid limitation and that appellants have failed to rebut that presumption.

We agree with appellants that the district court erred by applying prosecution history estoppel to the “blocking nucleic acid” limitation. “Prosecution history estoppel prevents a patentee from recapturing under the doctrine of equivalents subject matter surrendered during prosecution to obtain a patent.” Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 480 F.3d 1335, 1341 (Fed. Cir. 2007) (citing Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 741 (2002)). Thus, “a narrowing amendment made to satisfy any requirement of the Patent Act may give rise to an estoppel.” Festo, 535 U.S. at 736. “A patentee’s decision to narrow his claims through amendment may be presumed to be a general disclaimer of the territory between the original claim and the amended claim.” Id. at 740. The presumption of surrender, however, “may be rebutted if the patentee can demonstrate that: (1) the alleged equivalent would have been unforeseeable at the time . . . the narrowing amendment was made; (2) the rationale underlying the narrowing amendment bore no more than a tangential relation to the equivalent at issue; or (3) there was some other reason suggesting that the patentee could not reasonably have been expected to have described the alleged equivalent.” Honeywell Int’l Inc. v. Hamilton Sundstrand Corp., 370 F.3d 1131, 1140 (Fed. Cir. 2004) (quotations omitted).

In the present case, the prosecution history reveals that claim 1 of the '841 patent was amended for a substantial reason related to patentability. In the '841 patent application, the patentees filed claims that were directed to general methods of disabling the hybridization capacity of repetitive sequences, and also submitted a claim that specifically recited blocking nucleic acids. In particular, the patentees' application claims 28 and 99 read as follows:

28. (Twice amended) A method of staining chromosomal DNA that can be used to stain a particular chromosome type or portion thereof, or a particular group of chromosome types or portions thereof, whether the targeted chromosomal sequences are present at normal copy numbers for diploid or haploid cells or at higher copy numbers, the method comprising the steps of:

providing a heterogeneous mixture that contains labeled nucleic acid fragments that are substantially complementary to unique sequence regions of complexity of at least 35 kilobases (kb) in the targeted chromosomal DNA[;]

disabling the hybridization capacity of repetitive sequences within said heterogeneous mixture;

reacting the heterogeneous mixture with the target chromosomal DNA by *in situ* hybridization; and

rendering visible the hybridized, labeled fragments.

99. The method of staining chromosomal DNA according to Claim 28 wherein said disabling step includes substantially blocking the labeled repetitive nucleic acid fragments in the heterogeneous mixture by hybridization with unlabeled repetitive nucleic acid fragments that are complementary to those in the heterogeneous mixture.

J.A. 221, 238 (emphases added). The examiner issued several rejections of those claims for, inter alia, indefiniteness, anticipation, and obviousness. Thereafter, on February 5, 1993, the examiner conducted a personal interview with one of the inventors and his counsel. The Examiner Interview Summary Record indicates that

they discussed ways to distinguish the instant invention from certain prior art references and further discussed a “proposed claim directed solely to the use of blocking nucleic acids to direct probe hybridization to unique segments.” That claim, claim 132, read:

132. A method of staining chromosomal DNA comprising:

(a) providing 1) labeled nucleic acid that comprises fragments which are substantially complementary to nucleic acid sequences within the chromosomal DNA for which staining is desired, and 2) blocking nucleic acid that comprises fragments which are substantially complementary to repetitive sequences in the labeled nucleic acid;

(b) employing said labeled nucleic acid, blocking nucleic acid, and chromosomal DNA in *in situ* hybridization so that labeled repetitive sequences are substantially blocked from binding to the chromosomal DNA, while allowing substantial hybridization of unique sequences within the labeled nucleic acid to the chromosomal DNA.

Id. at 348 (emphases added). In filing that amendment, the patentees stated that the claims of the '841 patent would be limited to the embodiment involving the blocking method and that claims to other embodiments, including the embodiment involving the removal of repetitive sequences, would “be pursued in a separate application,” leading to the '479 patent. Because the prosecution history suggests that the patentees limited the claim to the blocking method at least in part to overcome the examiner’s rejections, the patentees presumptively surrendered all equivalents of the “blocking nucleic acid” limitation.

However, even if the Festo presumption applies, we must consider whether appellants rebutted the “presumption of total surrender by demonstrating that it did not surrender the particular equivalent in question.” Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd., 344 F.3d 1359, 1367 (Fed. Cir. 2003). Appellants rely on the tangential ground in support of their assertion that the presumption has been

rebutted. “[T]he inquiry into whether a patentee can rebut the Festo presumption under the ‘tangential’ criterion focuses on the patentee’s objectively apparent reason for the narrowing amendment.” Id. at 1369. Indeed, prosecution history estoppel will not bar the doctrine of equivalents when “the reason for the narrowing amendment was peripheral, or not directly relevant, to the alleged equivalent.” Id.

Here, the patentees identified two main reasons for the narrowing amendment. First, the patentees narrowed the claims in order to “facilitate prosecution.” In deciding to limit the claims of the ’841 patent to the blocking method and to pursue other means of disabling in a separate application, the patentees argued that “[b]y separating the different inventions into separate applications, it is believed that prosecution will be facilitated.” Such a reason for amending the claim is clearly nonsubstantive and does not help us in our analysis.

Second, and more significantly, however, the patentees did amend the claim in order to distinguish the invention over the prior art. The examiner issued prior art rejections in view of, inter alia, Weissman et al., Sealey et al., and Yunis et al. To overcome those references, the patentees argued that the invention was new and nonobvious because it used the blocking method in connection with in situ hybridization for the detection of unique sequences. In contrast, the Weissman reference involved the use of pure unique sequence probes—or probes from which repetitive sequences have been removed—as opposed to blocking. Both the Sealey and Yunis references, however, disclosed the use of the blocking method, but that method was limited to testing the hybridization of repetitive sequences and did not concern targeting unique sequences, as does the claimed use of blocking nucleic acids. As such, the patentees

argued that the invention would not have been obvious in view of the prior art because a person of ordinary skill would not have considered the use of blocking for the detection of unique sequences.

The prosecution history therefore reveals that in narrowing the claim to overcome the prior art rejections, the focus of the patentees' arguments centered on the method of blocking—not on the particular type of nucleic acid that could be used for blocking. Indeed, the “nucleic acid” limitation was never narrowed during prosecution and was not at issue in the office action rejecting the claims, the Examiner Interview Summary Record, or the patentees’ remarks accompanying the amendment. Moreover, Dako does not dispute that none of the cited references concerned the type of nucleic acid that could perform the blocking, or mentioned the accused equivalent. We thus conclude that appellants have met their burden of showing that the amendment did not surrender the equivalent in question because the narrowing amendment was only tangential to the accused PNA equivalent, *i.e.*, the peptide nucleic acid. Accordingly, the court erred in concluding that appellants are precluded by estoppel from asserting that Dako’s products infringe under the doctrine of equivalents. Whether they do infringe is a question of fact for the trial court to consider on remand.

### C. Remaining Issue in the Preliminary Injunction Appeal

Appellants presented two issues in their preliminary injunction appeal—both involving claim construction. The first issue related to the construction of the “heterogeneous mixture” limitation, which we have already dealt with. The district court denied appellant’s motion for a preliminary injunction upon concluding, *inter alia*, that appellants failed to show a likelihood of success that the sole product at issue, *viz.*,

Dako's HER2 kit, met the "heterogeneous mixture" limitation of the '479 patent. In light of our affirmance of the court's construction, we affirm the court's denial of the preliminary injunction.

Appellants also appeal the construction of another claim term that the court construed in its preliminary injunction order, viz., "morphologically identifiable cell nucleus." While we need not reach that issue in light of our affirmance of the denial of the preliminary injunction on the heterogeneous mixture ground, we will do so in the interest of judicial efficiency, as the issue has been fully briefed and that term will likely be at issue on remand.

The disputed claim term "morphologically identifiable cell nucleus" appears in both the '841 and '479 patents. The district court construed that term as "a single cell nucleus that contains the full complement of chromosomal DNA." Appellants argue that that construction is incorrect based on the specification and prosecution history of the patents. According to appellants, the claim merely requires that the nucleus be "capable of being identified by its form or function" and does not require the full set of DNA.

In response, Dako argues that the intrinsic evidence supports the court's construction. Dako asserts that the patentees characterized the invention as one that allows the detection of chromosomal abnormalities on a cell-by-cell basis and thus a full set of chromosomal DNA is required to achieve that objective.

We agree with appellants that the district court erred in its construction of this term. First, the plain language of the claim term "morphologically identifiable cell nucleus" suggests that the nucleus must be identifiable by form or structure, and does

not indicate that a full set of chromosomal DNA must be present in the cell nucleus. Appellants note, and Dako does not dispute, that the word “morphological” generally refers to form or structure, not to identity of chromosomal DNA content.

In addition, the prosecution history of the ’841 patent reveals that the term “morphologically identifiable cell nucleus” was added to the claim to clarify that the target chromosomal DNA remained in a natural biological structure during *in situ* hybridization. Indeed, the patentees argued that:

The [addition of the “morphologically identifiable” language] addresses the Examiner’s concern that the chromosomal DNA could have been taken from a chromosome but processed prior to hybridization. It makes clear that the *in situ* hybridization is conducted while the DNA is still present in a morphologically recognizable chromosome or cell nucleus.

J.A. at 447. Thus, by adding the disputed phrase, the patentees clarified that “the *in situ* hybridization is conducted while the DNA is still present in a morphologically identifiable chromosome or cell nucleus.” The implication of that statement is that while the DNA is still present, the identification is morphological, not by DNA identity. The patentees contrasted that method with other methods, such as “Southern blot hybridization in which the biological structure has been destroyed, and the DNA has been cut into restriction fragments and separated by size.” Significantly, nowhere in the prosecution history, or the specification for that matter, do we find any indication that the “morphologically identifiable” language was added to impose a requirement that the cell nucleus must retain its full complement of chromosomal DNA. Accordingly, the proper construction of “morphologically identifiable cell nucleus” is one that is capable of being identified by its form or structure—a construction that we find to be consistent with the intrinsic evidence.

## CONCLUSION

For the foregoing reasons, we affirm the district court's denial of the preliminary injunction, affirm in part the court's grant of summary judgment of noninfringement as to the '479 patent, and reverse in part the court's grant of summary judgment of noninfringement as to the '841 patent with respect to the HER2 and TOP2A products. We affirm the court's construction of "heterogeneous mixture of labeled unique sequence nucleic acid fragments," reverse the court's conclusion that appellants are estopped from asserting that Dako's products meet the "blocking nucleic acid" limitation under the doctrine of equivalents, and reverse the court's construction of "morphologically identifiable cell nucleus." The case is remanded to the district court for further proceedings consistent with this opinion.

## AFFIRMED IN PART, REVERSED IN PART, and REMANDED

## COSTS

No costs.

# **United States Court of Appeals for the Federal Circuit**

2006-1334, -1452

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA,  
ABBOTT MOLECULAR, INC., and ABBOTT LABORATORIES, INC.,

Plaintiffs-Appellants,

v.

DAKOCYTOMATION CALIFORNIA, INC.,

Defendant-Appellee.

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2007-1202

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA,  
ABBOTT MOLECULAR, INC., and ABBOTT LABORATORIES, INC.,

Plaintiffs-Appellants,

v.

DAKO A/S,  
and DAKO NORTH AMERICAN, INC.,

Defendants-Appellees.

Appeal from the United States District Court for the Northern District of California  
in case no. 05-CV-03955, Judge Marilyn Hall Patel.

PROST, Circuit Judge, dissenting-in-part.

I join the majority opinion except for Part B.2 of the Discussion section, reversing the district court and holding that the doctrine of equivalents is not precluded by prosecution history estoppel because the tangential exception applies, from which I respectfully dissent. The majority concludes that, by amending the claims, the

patentees surrendered all other methods of disabling the hybridization capacity of repetitive sequences, but did not surrender equivalents of the nucleic acid that could be used to perform the blocking. In my view, this conclusion is contrary to this court's precedent and to the proper application of prosecution history estoppel as set forth by the Supreme Court.

Under Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co. ("Festo I"), if the patentee narrows the scope of the claims of the patent in response to a rejection during prosecution, there is a presumption that the patentee is estopped from arguing that the surrendered territory comprises an equivalent for the purposes of infringement under the doctrine of equivalents. 535 U.S. 722, 739-40 (2002); see Int'l Rectifier Corp. v. IXYS Corp., Nos. 2007-1063, -1141, -1165, slip op. at 7 (Fed. Cir. Feb. 11, 2008). Prosecution history estoppel applies to any narrowing amendment made for a substantial reason related to patentability. Festo I, 535 U.S. at 739-40. The majority recognizes that the amendment here was made in order to overcome certain prior art references and, thus, the amendment was made for a substantial reason related to patentability. A narrowing amendment is all that is required for the presumption of prosecution history estoppel to attach to bar the application of the doctrine of equivalents.

The presumption of prosecution history estoppel with regard to a narrowing amendment is absolute, i.e., an amendment is "presumed to be a general disclaimer of the territory between the original claim and the amended claim." Festo I, 535 U.S. at 740; Biagro W. Sales, Inc. v. Grow More, Inc., 423 F.3d 1296, 1305 (Fed. Cir. 2005); Terlep v. Brinkmann Corp., 418 F.3d 1379, 1385 (Fed. Cir. 2005). The fact that

narrowing the claim to a method of blocking with a “blocking nucleic acid” may not have been necessary to distinguish over the prior art does not change the analysis. As this court has previously stated:

[T]here is no principle of patent law that the scope of a surrender of subject matter during prosecution is limited to what is absolutely necessary to avoid a prior art reference that was the basis for an examiner’s rejection. To the contrary, it frequently happens that patentees surrender more through amendment than may have been absolutely necessary to avoid particular prior art. In such cases, we have held the patentees to the scope of what they ultimately claim, and we have not allowed them to assert that claims should be interpreted as if they had surrendered only what they had to.

Norian Corp. v. Styker Corp., 432 F.3d 1356, 1361-62 (Fed. Cir. 2005). Here, the amendment narrowed the scope of the invention from any method of disabling the hybridization capacity of repetitive sequences to a method of disabling repetitive sequences using “blocking nucleic acids.” The parties have stipulated that “blocking nucleic acid” means “fragments of repetitive-sequence-enriched DNA or RNA.” Therefore, the patentee surrendered all other methods for disabling hybridization capacity of repetitive sequences including methods of blocking other than with DNA or RNA. It is irrelevant to the determination of the scope of the surrendered territory that to overcome the prior art references the patentee did not need to amend the claims to a method of disabling the hybridization capacity of repetitive sequences by blocking with a “blocking nucleic acid,” but instead could have amended the claims to a method of disabling repetitive sequences by blocking.

Under Festo I, the presumption of a wholesale surrender of territory between the original claim and the amended claim may only be rebutted if the patentee is able to show that one of the exceptions applies. 535 U.S. at 740-41. The appellants do not

suggest that this case falls under the “some other reason” exception. The appellants do not and cannot assert the “unforeseeable” exception since PNAs were discovered prior to when the narrowing amendment was made. See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co. (“Festo II”), 344 F.3d 1359, 1369 (Fed. Cir. 2003). Rather, before the district court and on appeal, the appellants raised only the tangential exception. The majority agrees that the tangential exception bars application of prosecution history estoppel. In so concluding, they reason that the patentee, in narrowing the claims to overcome the prior art, focused on the method of blocking and not on the particular type of nucleic acid that could be used in the blocking.

“[T]he inquiry into whether a patentee can rebut the Festo presumption under the ‘tangential’ criterion focuses on the patentee’s objectively apparent reason for the narrowing amendment.” Id. The primary consideration is “whether the amendment is peripheral or not directly relevant, to the alleged equivalent.” Id. Here, the reason for the amendment bears more than a tangential relationship to the equivalent. The amendment limits the claims to a method of disabling repetitive sequences by blocking with “blocking nucleic acids” (i.e., DNA or RNA). In making the amendment, the appellants presumptively surrendered any other means of disabling repetitive sequences. The equivalent, PNA, however, functions to do exactly that, i.e., to disable repetitive sequences. Hence, the purpose for the amendment is not unrelated to the equivalent. See Int'l Rectifier, slip op. at 9-10; Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 480 F.3d 1335, 1343 (Fed. Cir. 2007); Biagro, 423 F.3d at 1306; Terlep, 418 F.3d at 1379; Rhodia Chimie v. PPG Indus. Inc., 402 F.3d 1371, 1383 (Fed. Cir. 2005).

The appellants rely on two cases to support application of the tangential exception, Insituform Technologies, Inc. v. CAT Contracting, Inc., 385 F.3d 1360 (Fed. Cir. 2004), and Primos, Inc. v. Hunter's Specialties, Inc., 451 F.3d 841 (Fed. Cir. 2006). However, this case is distinguishable from both of those cases. The patent at issue in Insituform was directed to a method for performing pipe repair without removing the damaged pipe from the ground. 385 F.3d at 1362. The patented method comprised impregnating a curable resin to the inside of the tube while applying a vacuum. Id. at 1368-69. The original claims did not specify the position or number of vacuum cups. Id. at 1369. The prior art method suffered from the problem that the vacuum was at the far end of the tube opposite the resin source and required an exceedingly large suction compressor. Id. To overcome the prior art, the patent claims were amended to specify that the vacuum source was close to the resin source. Id. at 1369-70. The alleged equivalent differed from the claimed method only in that it used multiple vacuum cups. Id. at 1369. Thus, we held that the narrowing amendment was tangential to the equivalent, which used multiple cups. Id. at 1370.

In Primos, the patent was directed to a diaphragm mouth call used by hunters to simulate animal sounds. 451 F.3d at 843. The prior art device contained a shelf structure which was directly above the membrane with no space in between. Id. at 849. During prosecution, the claims were amended to add a limitation requiring that the plate be "differentially spaced" above the membrane. Id. The alleged equivalent contained a dome, instead of a plate, which was similarly spaced above the membrane. Id. We concluded, therefore, that the equivalent (dome as opposed to plate) was tangential to

the purpose of the amendment, which was to require spacing between the plate and the membrane. Id.

In both Insituform and Primos, “the reason for the amendment and the alleged equivalent involved different aspects of the invention.” Biagro, 423 F.3d at 1306. Here, the purpose for the amendment and the accused equivalent do not involve different aspects of the invention. Indeed, they both relate to the means for disabling repetitive sequences. Therefore, the equivalent is not tangential to the purpose for the amendment. To overcome the presumption of prosecution history estoppel “[t]he patentee must show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent.” Festo I, 535 U.S. at 741. Here, the appellants could reasonably have been expected to have drafted a claim that encompassed blocking repetitive sequences using PNA. The appellants should, therefore, be estopped from asserting that PNA is an equivalent to “blocking nucleic acid” in the ’841 patent.

For these reasons, I respectfully dissent.