United States Court of Appeals for the Federal Circuit

2009-1281

ENZO BIOCHEM, INC., ENZO LIFE SCIENCES, INC.,
and YALE UNIVERSITY,

Plaintiffs-Appellants,

v.

APPLERA CORP. and TROPIX, INC.,

Defendants-Appellees.

L. Gene Spears, Baker Botts L.L.P., of Houston, Texas, argued for plaintiffs-appellants. With him on the brief was Michael A. Hawes.

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

Judge Janet Bond Arterton

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Defendants-Appellees.

Appeal from the United States District Court for the District of Connecticut in case no. 3:04-CV-929, Judge Janet Bond Arterton.

DECIDED: March 26, 2010

Before MICHEL, Chief Judge, PLAGER, and LINN, Circuit Judges.

LINN, Circuit Judge.

Enzo Biochem, Inc., Enzo Life Sciences, Inc., and Yale University (collectively, "Enzo") appeal the grant of summary judgment by the U.S. District Court for the District of Connecticut in favor of Applera Corp. and Tropix, Inc. (collectively, "Applera") that all asserted claims of U.S. Patents No. 5,328,824 ("the '824 patent"), No. 5,449,767 ("the '767 patent"), and No. 5,476,928 ("the '928 patent") are invalid as either indefinite or anticipated, and that U.S. Patent No. 5,082,830 ("the '830 patent") is not infringed. Enzo Biochem, Inc. v. Applera Corp., No. 3:04-CV-929 (D. Conn. Mar. 5, 2009). Because we conclude that the claims of the '824 and '767 patents are not indefinite, and because we find genuine issues of material fact as to anticipation, we reverse the

district court's summary judgment of invalidity of those two patents. Although we find that the '928 patent is not indefinite, we affirm the district court's judgment of anticipation as to that patent. Because the district court correctly construed the claims of the '830 patent, under which the patent is not infringed, we affirm the judgment of noninfringement. The case is remanded.

BACKGROUND

Enzo's patents-in-suit are directed to various techniques for labeling and detecting nucleic acids, such as DNA and RNA. To put the analysis in context, we begin with a brief discussion of the basic technology and vocabulary related to this case and undisputed by the parties.

I. Basic Technology and Vocabulary

DNA and RNA are composed of a series of units, called "nucleotides." Each nucleotide is composed of a nitrogenous base, a pentose sugar, and a phosphate group. The phosphate group of one nucleotide forms a covalent bond with the pentose sugar of an adjacent nucleotide, thereby linking the nucleotides along a "sugar-phosphate backbone." Aside from linking the nucleotide units into a polynucleotide strand, the sugar-phosphate backbone provides structural support for the nitrogenous bases. The bases fall into two categories: pyrimidines and purines. Pyrimidines include cytosine ("C"), thymine ("T"), and uracil ("U"). Purines include adenine ("A") and guanine ("G"). DNA contains the bases adenine, thymine, cytosine, and guanine; RNA also includes adenine, cytosine, and guanine, but contains the base uracil in place of thymine. Two strands of DNA or RNA having complementary bases will bind, or "hybridize," to form a double-stranded complex, or "hybrid," which is held together by

hydrogen bonds between complementary bases. In DNA, adenine on one strand binds to thymine on the other; in RNA, adenine binds to uracil; and in both DNA and RNA, cytosine binds to guanine. The process of forming a double-stranded hybrid is called "hybridization." The reverse process, resulting in two separate strands, is called "denaturation."

Because hybridization occurs in a predictable manner between complementary strands, it is possible to detect the presence of a nucleic acid of interest in a sample. For example, a chemical entity, called a "label," can be attached to or incorporated into a nucleic acid strand of a known sequence, called a "probe," which will hybridize with a complementary sequence of interest, called a "target." Once the probe is hybridized with the target, a detectable signal is generated either from the label itself (referred to as "direct detection") or from a secondary chemical agent that is bound to the label (referred to as "indirect detection"). If a signal is detected from the sample after all unhybridized probes have been removed, detection of the signal implies the presence of a target in that sample.

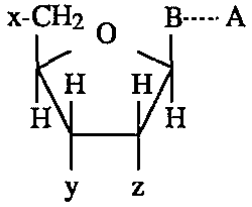
Labeling of nucleic acids has been accomplished using a variety of chemical entities. For example, with radioactive labels, an isotope of hydrogen (^{3}H), phosphorous (^{32}P), or carbon (^{14}C) is substituted for a non-radioactive atom within the probe, and the isotope is then detected using a radiation detector. But radioactive labels have drawbacks. As explained in the '824, '767, and '928 patents, radioactive

labels are "potentially hazardous," "expensive to purchase and use," and "often very unstable." '824 patent col.1 ll.34-45.[1]

To avoid these drawbacks, the inventors of the patents-in-suit developed a series of nucleotide probes that do not rely on traditional radioactive labels. The '824, '767, and '928 patents are directed to these developments and all claim priority to an application filed on April 17, 1981. The '830 patent issued from an application filed on February 26, 1988 and is directed to improvements over some of the probes claimed in the earlier patents.

II. The '824, '767, and '928 Patents

In general, the claims of the '824, '767, and '928 patents are directed to a "compound" (whose structure is depicted below), or a method of using that compound as a detection probe. In this compound, a nitrogenous base "B" is covalently attached, either directly or through a "linkage group" (represented by the dotted line), to a chemical moiety "A."



The "linkage group" is not recited in the independent claims in structural terms. Rather, the linkage group is recited functionally as "not interfering substantially" with both hybridization and detection ('824 and '767 patents) or simply detection ('928 patent). See '824 patent col.31 ll.31-34 ("said linkage group not interfering substantially

[1] Because the '824, '767, and '928 patents share a common specification, we shall cite the '824 patent when referencing the common specification.

with the characteristic ability of said compound to hybridize with said nucleic acid or of A to be detected" (emphases added)); '767 patent col.31 ll.2-7 ("a linkage group that does not substantially interfere with the characteristic ability of the oligo- or polynucleotide to hybridize with a nucleic acid and does not substantially interfere with formation of the signalling moiety or detection of the detectable signal" (emphases added)); '928 patent col.30 ll.29-30 ("said linkage group not interfering substantially with detection of A" (emphasis added)). The specification describes the function of the linkage group as follows:

> [I]t is generally preferred that the chemical linkage include an olefinic bond at the α-position relative to B . . . . [Which] serves to hold the moiety A away from the base when the base is paired with another in the well known double-helix configuration. This permits interaction with polypeptide to occur more readily, thereby facilitating complex formation. Moreover, single bonds with greater rotational freedom may not always hold the moiety sufficiently apart from the helix to permit recognition by and complex formation with polypeptide.

'824 patent col.8 ll.54-68.

The chemical moiety A is the label that facilitates detection. In claim 1 of the '824 and '767 patents, moiety A "comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing a detectable signal." In claim 1 of the '928 patent, moiety A "represents at least three carbon atoms and an indicator molecule selected from the group consisting of fluorescent dyes, electron-dense reagents, enzymes which can be reacted with a substrate to produce a visually detectable reaction product, and radioisotopes."

The symbols "x," "y," and "z" represent, variously, one of the following: hydrogen, hydroxyl, or one or more components of the sugar-phosphate backbone.

III. The ’830 Patent

The later-filed ’830 patent contains claims to both a compound and a method of detection using that compound. The claimed compound is a nucleotide labeled with “at least one non-radioactive moiety directly or indirectly attached to each of the 5′ and 3′ end nucleotides thereof.” ’830 patent col.13 ll.63-65, col.14 ll.58-61. The 5′ and 3′ positions are locations on a pentose sugar: the 5′ end is the so-called “left” end of the polymer; the 3′ end is the so-called “right” end of the polymer. In the method claim, a “target” strand is contacted under hybridization conditions with both (i) a “probe” strand having 5′ and 3′ labels and (ii) a “preformed detectable molecular complex.” Id. col.14 ll.53-64. Detection is accomplished by “detecting any hybridized complexes.” Id. col.14 ll.65-66.

IV. Proceedings Below

On June 7, 2004, Enzo sued Applera for infringement of six patents, four of which are here on appeal.[2] The asserted claims of the four patents on appeal are: claims 1, 18, 19, 21, 26, 28, 32, and 33 of the ’824 patent; claims 1, 2, 8, 11, 13, 42, 46-51, 67, 68, and 70 of the ’767 patent; claims 1 and 2 of the ’928 patent; and claims 1, 12, and 18 of the ’830 patent.

The district court issued a claim construction ruling on October 12, 2006. Enzo Biochem, Inc. v. Applera Corp., No. 04-929, 2006 WL 2927500 (D. Conn. Oct. 12, 2006) (“Claim Construction”). With regard to the linkage group in each of the ’824, ’767, and ’928 patents, the district court construed the “not interfering substantially” language to mean that “the linkage group neither substantially interferes with the ability of the

[2] The unappealed patents are U.S. Patents No. 4,711,955 and No. 4,994,373.

compound to hybridize with the nucleic acid nor substantially interferes with the ability of A to be detected." Id. at *6. With regard to the moiety A, the district court found the differing claim language of the '824, '767, and '928 patents to be relevant to whether A constitutes the whole or merely a portion of the entity that produces a detectable signal. More specifically, with regard to the '824 and '767 patents, the district court held that "A may be a part of or the entire signalling moiety," and therefore adopted Enzo's proposed construction that "A comprises at least three carbon atoms and is one or more parts of a signalling moiety, which includes, in some instances, the whole signalling moiety." Id. at *4. By contrast, the district court held that the plain language of the '928 patent "precludes a construction where A is the entire [indicator] molecule," and therefore adopted Applera's proposed construction that "A must have at least three carbon atoms and an indicator molecule selected from the group consisting of (i) fluorescent dyes, (ii) electron-dense reagents, (iii) enzymes which can be reacted with a substrate to produce a visually detectable reaction product, or (iv) radioisotopes." Id. at *5. Finally, as to the "non-radioactive moiety" of the '830 patent, because the claims call for the use of a "detectable molecular complex," the district court construed "non-radioactive moiety" to mean "a moiety that is utilized in indirect detection, i.e., a moiety that can be detected with a preformed detectable molecular complex." Id. at *11.

Enzo conceded that under the district court's construction it could not prove infringement of the '830 patent. Based on this concession, the district court granted summary judgment of noninfringement of the '830 patent on August 7, 2007. Applera then moved for summary judgment of invalidity of all asserted claims of the '824, '767, and '928 patents based on: (1) lack of written description under 35 U.S.C. § 112, ¶ 1;

(2) lack of enablement under 35 U.S.C. § 112, ¶ 1; (3) indefiniteness under 35 U.S.C. § 112, ¶ 2; and (4) anticipation under 35 U.S.C. § 102.

On September 6, 2007, the district court denied Applera's summary judgment motion as to lack of written description and enablement, but granted the motion as to indefiniteness and anticipation. Enzo Biochem, Inc. v. Applera Corp., No. 3:04-CV-929, 2007 WL 2669025 (D. Conn. Sept. 6, 2007) ("Summary Judgment"). With regard to indefiniteness, the district court held that the "not interfering substantially" language in the asserted claims of all three patents is indefinite because "[t]he specifications neither set forth how one would gauge substantial interference, nor delimit the threshold at which interference with the procedure prevents [the claimed] method from being implemented." Id. at *12. Alternatively, the district court found these same claims to be anticipated by at least one of three prior art references.[3] In concluding that there was no genuine issue of material fact that the prior art taught a linkage group that did "not substantially interfere" with hybridization and detection, the district court observed that "[a]lthough this Court has determined that the 'substantially interfere' language in the ['824, '767, and '928 p]atents is the basis for their invalidity, interpretation of the phrase for purposes of anticipation does not affect the invalidity ruling." Id. at *13. Thus, on

[3] The three prior art references are: Hiroshi Kasai et al., Specific fluorescent labeling of 7-(aminomethyl)-7-deazaguanosine located in the anticodon of $tRNA^{Tyr}$ isolated from E. coli mutant, 7 Nucleic Acids Res. 231 (1979) ("Kasai"); Alfred Pingoud et al., Fluoresceinylthiocarbamyl-$tRNA^{Tyr}$: a useful derivative of $tRNA^{Tyr}$ (E.coli) for physiochemical studies, 4 Nucleic Acids Res. 327 (1977) ("Pingoud"); J.G.J. Bauman, Cytochemical Detection of Specific Nucleic Acid Sequences Development and Application of In Situ Hybridisation Methods for Fluorescence Microscopy (doctoral thesis publ. Drukkerji J.H. Pasmans b.v. 's-Gravenhage, Netherlands (1980)) ("Bauman").

summary judgment, all asserted claims of the '824, '767, and '928 patents were held invalid as either indefinite or anticipated.

The district court entered final judgment with respect to all six patents on March 5, 2009. Enzo appeals the final judgment with respect to the '824, '767, '928, and '830 patents. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

"A determination that a patent claim is invalid for failing to meet the definiteness requirement in 35 U.S.C. § 112, ¶ 2 is a legal question reviewed de novo." Young v. Lumenis, Inc., 492 F.3d 1336, 1344 (Fed. Cir. 2007). "Because a patent is presumed to be valid, the evidentiary burden to show facts supporting a conclusion of invalidity is one of clear and convincing evidence." Id. at 1345. "We review a district court's grant of summary judgment de novo, reapplying the standard applicable at the district court." Id. "While anticipation is a question of fact, 'it may be decided on summary judgment if the record reveals no genuine dispute of material fact.'" Leggett & Platt, Inc. v. VUTEk, Inc., 537 F.3d 1349, 1352 (Fed. Cir. 2008) (quoting Golden Bridge Tech., Inc. v. Nokia, Inc., 527 F.3d 1318, 1321 (Fed. Cir. 2008)). Summary judgment is appropriate "if the pleadings, the discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c)(2).

I. The '824, '767, and '928 Patents

Enzo challenges the district court's grant of summary judgment that all asserted claims of the '824, '767, and '928 patents are invalid in the alternative—as indefinite, but if not indefinite, then invalid as anticipated. As a preliminary matter, we observe that a

claim cannot be both indefinite and anticipated. A determination that a claim is anticipated involves a two-step analysis: "the first step requires construing the claim," and "[t]he second step in the analysis requires a comparison of the properly construed claim to the prior art . . . ." Power Mosfet Techs., LLC v. Siemens AG, 378 F.3d 1396, 1406 (Fed. Cir. 2004). If a claim is indefinite, the claim, by definition, cannot be construed. Without a discernable claim construction, an anticipation analysis cannot be performed. See Honeywell Int'l, Inc. v. Int'l Trade Comm'n, 341 F.3d 1332, 1342 (Fed. Cir. 2003) (vacating finding of infringement entered after claims were properly held to be indefinite).

A. Indefiniteness

On appeal, Enzo first argues that the district court incorrectly determined that the "not interfering substantially" language in the '824, '767, and '928 patents is indefinite. In Enzo's view, the specifications provide specific examples of linkage groups that do not substantially interfere with hybridization and detection, as well as general criteria for selecting suitable linkage groups. Moreover, Enzo asserts that the specification provides a test for measuring the degree of interference, namely, comparing the thermal denaturation profile (i.e., melting temperature) of a modified polynucleotide with that of an unmodified polynucleotide.

Applera responds that the district court correctly determined that the "not interfering substantially" language is indefinite, arguing that nothing in the patents explains how to measure "interference" or how to determine whether it is "substantial." Because even a minor alteration of a single nucleotide may have profound effects on the ability of a DNA strand to hybridize, depending on the length and sequence of the

strand, Applera argues that identical linkage groups may cause interference in some strands but not in others, thus rendering the claims hopelessly ambiguous.

We agree with Enzo that the claims are not indefinite. "Indefiniteness requires a determination whether those skilled in the art would understand what is claimed. To make that determination, we have explained that '[i]n the face of an allegation of indefiniteness, general principles of claim construction apply.'" Young, 492 F.3d at 1346 (quoting Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1348 (Fed. Cir. 2005)). "In that regard, claim construction involves consideration of primarily the intrinsic evidence, viz., the claim language, the specification, and the prosecution history." Id. When a "word of degree" is used, the court must determine whether the patent provides "some standard for measuring that degree." Seattle Box Co., Inc. v. Indus. Crating & Packing, Inc., 731 F.2d 818, 826 (Fed. Cir. 1984). Similarly, when a claim limitation is defined in "purely functional terms," a determination of whether the limitation is sufficiently definite is "highly dependent on context (e.g., the disclosure in the specification and the knowledge of a person of ordinary skill in the relevant art area)." Halliburton Energy Servs., Inc. v. M-I LLC, 514 F.3d 1244, 1255 (Fed. Cir. 2008).

Because the claim language of the '824 and '767 patents differs from that of the '928 patent with regard to "hybridization" and "detection," we address these two terms separately.

1. Hybridization

The claims of the '824 and '767 patents provide that the linkage group must not substantially interfere with both hybridization and detection: '824 patent col.31 ll.31-34

("said linkage group not interfering substantially with the characteristic ability of said compound to hybridize with said nucleic acid or of A to be detected" (emphases added)); '767 patent col.31 ll.1-7 ("a linkage group that does not substantially interfere with the characteristic ability of the oligo- or polynucleotide to hybridize with a nucleic acid and does not substantially interfere with formation of the signalling moiety or detection of the detectable signal" (emphases added)). By contrast, the claims of the '928 patent provide only that the linkage group must not substantially interfere with detection: "said linkage group not interfering substantially with detection of A." '928 patent col.30 ll.28-30 (emphasis added)). The district court, however, adopted an identical construction for all three patents that refers to both hybridization and detection: "the linkage group neither substantially interferes with the ability of the compound to hybridize with the nucleic acid nor substantially interferes with the ability of A to be detected." Claim Construction, 2006 WL 2927500, at *6 (emphases added).

As a preliminary matter, we see no basis to read a "hybridization" requirement into the claims of the '928 patent. Nothing in the claims refers to hybridization, and neither the specification nor the prosecution history contains a clear disclaimer or a contrary definition regarding the "not interfering substantially" language that would require us to read such a requirement into the claims. The applicants knew how to claim a linkage group that does not substantially interfere with hybridization, as they did in the '824 and '767 patents, but specifically omitted that language from the claims of the related '928 patent. We therefore modify the construction of this limitation with regard to the '928 patent to read: "the linkage group does not substantially interfere with the ability of A to be detected."

With regard to the '824 and '767 patents, the term "hybridization" has a definite meaning. The district court correctly understood the term to mean "the binding of two separate, complementary strands of nucleic acids to form nucleic acid hybrids." Id. at *1 n.1. The ambiguity, in the district court's view, was that a person of ordinary skill would not understand whether a linkage group interferes with hybridization "substantially."

We begin with the language of the claims. The word "substantially," when used in a claim, can denote either language of approximation or language of magnitude. See Deering Precision Instruments, LLC v. Vector Distrib. Sys., Inc., 347 F.3d 1314, 1323 (Fed. Cir. 2003). As used in the phrase "not interfering substantially," the word "substantially" denotes language of magnitude because it purports to describe how much interference can occur during hybridization, i.e., an insubstantial amount of interference. See Epcon Gas Sys., Inc. v. Bauer Compressors, Inc., 279 F.3d 1022, 1031 (Fed. Cir. 2002) ("[T]he phrase 'substantially below' signifies language of magnitude, i.e., not insubstantial."). The claims in this case provide at least some guidance as to how much interference will be tolerated. A dependent claim in both patents specifies that the linkage group has a particular structure (–CH=CH–CH_2–NH–). See '824 patent col.32 ll.66-68; '767 patent col.31 ll.38-40. A person of ordinary skill would presume that a structure recited in a dependent claim will perform a function required of that structure in an independent claim. See AK Steel Corp. v. Sollac & Ugine, 344 F.3d 1234, 1242 (Fed. Cir. 2003) ("Under the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend."). Thus, it may be presumed that the term "not interfering substantially" in the independent claims allows for at least as much

interference as that exhibited when the linkage group has the structure specified in the dependent claims.[4]

The specification provides additional examples of suitable linkage groups, including some criteria for selecting them. After stating generally that the linkage group "may include any of the well known bonds including carbon-carbon single bonds, carbon-carbon double bonds, carbon-nitrogen single bonds, or carbon-oxygen single bonds," the specification goes on to note that "[i]t is even more preferred that the chemical linkage group be derived from a primary amine, and have the structure $–CH_2–NH–$, since such linkages are easily formed utilizing any of the well known amine modification reactions." '824 patent col.8 ll.54-58, col.9 ll.1-5. Moreover, one of the "essential criteria" of a modified polynucleotide noted in the specification is that "the linkage that attaches the probe moiety should withstand all experimental conditions to which normal nucleotides and polynucleotides are routinely subjected, e.g., extended hybridization times at elevated temperatures, phenol and organic solvent extraction, electrophoresis, etc." Id. col.6 l.29, col.7 ll.3-8.

The specification also teaches that the polynucleotides' "thermal denaturation profiles and hybridization properties" can be used to measure the degree to which a linkage group interferes with hybridization. Id. col.18 ll.61-62. Because hybridization occurs via hydrogen bonding between complementary bases, any interference in this

[4] Of course, if this particular embodiment is inoperable, because a linkage group having the structure $–CH=CH–CH_2–NH–$ entirely precludes hybridization, then the basis for invalidity would be a lack of enablement, not indefiniteness. Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1382 (Fed. Cir. 2001) (stating that inoperable embodiments present "an issue of enablement, and not indefiniteness"); Miles Labs., Inc. v. Shandon Inc., 997 F.2d 870, 875 (Fed. Cir. 1993) ("The invention's operability may say nothing about a skilled artisan's understanding of the bounds of the claim.").

bonding will result in weaker intermolecular forces and thus a lower melting temperature (T_m) of the hybrid. For example, the specification states that a DNA strand was modified by substituting every thymidine residue of the strand with a biotinyl-nucleotide. The resultant hybridization exhibited by the modified DNA strand was reported to be acceptable: "the T_m is only 5 °C less than that of the unsubstituted control." Id. col.19 ll.5-8 (emphasis added). A similar test was performed on poly d(A-bioU), in which every base pair contained a bio-dUMP residue. This modified polynucleotide showed a significantly lower T_m than the unsubstituted control, yet its hybridization was still deemed acceptable: "Although the T_m . . . is 15 °C lower than the poly d(A-T) control, the degree of cooperativity and the extent of hyperchromicity observed both during denaturation and renaturation were the same for the two polymers." Id. col.19 ll.9-14 (emphases added). Thus, as a general guideline, when a linkage group is incorporated into a DNA strand having a length and sequence similar to those used in the specification, a decrease in T_m of up to 5 °C implies that the linkage group does not "substantially interfere" with hybridization, and a decrease of up to 15 °C is acceptable if the degree of cooperativity and the extent of hyperchromicity are the same for the modified and unmodified strands.

The prosecution history of these patents is also helpful. Before the U.S. Patent and Trademark Office ("PTO"), Enzo overcame an indefiniteness rejection over the "not interfering substantially" language by submitting a declaration under 37 C.F.R. § 1.132, which was signed by its vice president, Dr. Engelhardt ("Engelhardt Declaration"), listing eight specific linkage groups that Enzo declared did not substantially interfere with hybridization or detection. Among the named linkage groups was –CH=CH–CH_2–NH–

(the same group recited in the patents' dependent claims) and –NH–$(CH_2)_6$–NH– (a new group that is not found in the specification and which contains only single bonds). J.A. 4320. Based on this submission, the examiner withdrew the indefiniteness rejection.

Because the intrinsic evidence here provides "a general guideline and examples sufficient to enable a person of ordinary skill in the art to determine [the scope of the claims]," In re Marosi, 710 F.2d 799, 803 (Fed. Cir. 1983), the claims are not indefinite even though the construction of the term "not interfering substantially" defines the term without reference to a precise numerical measurement, see Young, 492 F.3d at 1346 (holding that a word of degree was definite, even without a numerical claim construction); Exxon, 265 F.3d at 1381 (same); Marosi, 710 F.2d at 803 (same); In re Mattison, 509 F.2d 563, 565 (CCPA 1975) (same). When deciding whether a particular linkage group is or is not "substantially" interfering with hybridization within the meaning of the district court's construction, a person of ordinary skill would likely look to the thermal denaturation profiles and hybridization properties (including T_m) of the modified nucleotide, to see whether they fall within the range of exemplary values disclosed in the intrinsic evidence. See Young, 492 F.3d at 1346 (stating that a figure in the specification "provides a standard for measuring the meaning of the term 'near,'" even without a numerical claim construction); Exxon, 265 F.3d at 1380 (stating that a "period sufficient," recited in the claim, can be ascertained by performing activity checks).

Contrary to Applera's assertion, the fact that the binding strength of a DNA strand may vary, based on the length and sequence of the strand, does not mean that the choice of a linkage group will "depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention," as in Datamize. 417 F.3d at

1350. In Datamize, the invention was directed to a computer interface screen with an "aesthetically pleasing look and feel." Id. at 1344-45. The patentee sought a construction of the term "aesthetically pleasing" that depended solely on the subjective opinion of the person selecting features to be included on the interface screen. Nothing in the intrinsic evidence provided any guidance as to what design choices would result in an "aesthetically pleasing" look and feel. Id. at 1352. The claims were held indefinite because the very same interface screen may be "aesthetically pleasing" to one user but not to another.

Here, by contrast, the binding strength of a DNA strand will depend on the length and sequence of the strand, not on the subjective opinion of the particular chemist performing the hybridization. This is because, under a given set of experimental conditions, a DNA strand of a given length and sequence will have a fixed, measurable denaturation profile, which can be compared with the examples in the specification to determine whether interference with hybridization is substantial. The claims are not indefinite simply because the binding strength of a DNA strand will vary based on the strand's length and sequence. See Young, 492 F.3d at 1346 (holding claim definite even though "the size of the appendage and the amount of skin required to be incised will vary from animal to animal based on the animal's size").

Thus, we hold that the claim language regarding "hybridization" is not indefinite.

2. Detection

With regard to "detection," we agree with Enzo that the claims are not indefinite for most of the same reasons discussed in connection with "hybridization." The eight linkage groups listed in the Rule 132 declaration were said not to "interfere[] with the

ability of biotin in an oligo- or polynucleotide probe of this invention to form a detectable complex with one of avidin, streptavidin or antibodies to biotin or iminobiotin." J.A. 4318. According to the specification, when biotin is used as the moiety A, the resultant complexes can be detected "by means of conventional detection techniques." '824 patent col.18 ll.4-6. So long as moiety A can be detected within the level of detection achieved by the applicants using the exemplary linkage groups disclosed in the intrinsic evidence, a person of ordinary skill would understand that a different linkage group (one that is not disclosed in the intrinsic evidence) likewise does not "substantially interfere" with the detection of moiety A. The claims are not indefinite even if some experimentation is required to determine the exact level of detection achieved by the applicants using their exemplary linkage groups. See Exxon, 265 F.3d at 1379 ("Provided that the claims are enabled, and no undue experimentation is required, the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite.").

* * *

For the foregoing reasons, we conclude that the "not interfering substantially" language in the '824, '767, and '928 patents is not indefinite.

B. Anticipation

The district court granted Applera's motion for summary judgment that (1) Kasai anticipates the asserted claims of the '824 and '767 patents, (2) Pingoud anticipates the asserted claims of the '767 patent, and (3) Bauman anticipates the asserted claims of the '928 patent. On appeal, Enzo argues that none of the references disclose a "linkage

group" that does not substantially interfere with hybridization, and that the testimony of its expert, Dr. Sherman, was sufficient to create a genuine issue of material fact.

In moving for summary judgment on an issue as to which Applera bore the burden of persuasion, Applera supported its motion with detailed claim charts showing where each and every claim limitation is disclosed in the prior art, and an expert declaration explaining how the prior art meets those limitations under the district court's claim construction. See Saab Cars USA, Inc. v. United States, 434 F.3d 1359, 1369 (Fed. Cir. 2006) (party with the burden of persuasion on an issue must "provide evidence sufficient, if unopposed, to prevail as a matter of law"); 11 James Wm. Moore, Moore's Federal Practice § 56.13[1] (3d ed. 2009) ("[I]f the movant has the burden of persuasion on an issue, the movant must make a stronger claim to summary judgment by introducing supporting evidence that would conclusively establish movant's right to a judgment after trial should nonmovant fail to rebut the evidence."). With respect to the "linkage group" limitation, two of Applera's prior art references (Kasai and Pingoud) employ a $–CH_2–NH–$ linkage group, which arguably belongs to the set of linkage groups disclosed in the patents-in-suit as "even more preferred" embodiments. '824 patent col.9 ll.1-5 ("It is even more preferred that the chemical linkage group be derived from a primary amine, and have the structure $–CH_2–NH–$, since such linkages are easily formed utilizing any of the well known amine modification reactions."). Moreover, all three of Applera's references, on their face, report the ability to detect the presence of moiety A. If unopposed, this evidence would entitle Applera to judgment as a matter of law. We therefore agree with the district court that Applera carried its initial burden of making a prima facie showing of anticipation.

"When a motion for summary judgment is properly made and supported, an opposing party may not rely merely on allegations or denials in its own pleading; rather, its response must—by affidavits or as otherwise provided in this rule—set out specific facts showing a genuine issue for trial." Fed. R. Civ. P. 56(e)(2). The requirement that the nonmovant must set forth "specific facts" means that "[m]ere denials or conclusory statements are insufficient" to survive summary judgment. Barmag Barmer Maschinenfabrik AG v. Murata Machinery, Ltd., 731 F.2d 831, 836 (Fed. Cir. 1984). The standard on this issue is the same in the Second Circuit, see Davis v. New York, 316 F.3d 93, 100 (2d Cir. 2002), which applies in this case "because the issue is a procedural matter not unique to patent law." Arthur A. Collins, Inc. v. N. Telecom Ltd., 216 F.3d 1042, 1048 (Fed. Cir. 2000).

After reviewing the material that Enzo submitted in opposition to Applera's summary judgment motion, we conclude that Enzo has raised a genuine issue of material fact as to Kasai and Pingoud sufficient to survive summary judgment of anticipation of the '767 and '824 patents. However, as discussed below, Enzo has failed to raise a genuine issue of material fact with respect to Bauman and the '928 patent.

1. Kasai

With respect to Kasai, Enzo offered the declaration of its expert, Dr. Sherman, who stated that Kasai's "aminomethyl group [(–CH_2–NH–)] would not provide sufficient rigidity to prevent significant interference with hybridization of a complementary polynucleotide. Indeed, one would predict based on the flexibility of this functional group and the concomitant high degree of motion, there would be significant

interference due to free rotation about the single bonds." Sherman Decl. ¶ 44. This is in contradistinction to a linkage group including a carbon-carbon double bond, which presumably would be sufficiently rigid to prevent significant interference with hybridization, because the bound elements would not be free to rotate about their axes and sterically interfere at the hybridization site.

During prosecution, Enzo submitted the Engelhardt Declaration, which listed eight suitable linkage groups that did not substantially interfere with hybridization or detection. Seven included a carbon-carbon double bond, and one, –NH–$(CH_2)_6$–NH–, consisted entirely of single bonds. Applera argues that Dr. Sherman's declaration cannot be credited because it conflicts with Dr. Engelhardt's declaration that an all-single-bond linkage group was suitable. See Cleveland v. Policy Mgmt. Sys. Corp., 526 U.S. 795, 806 (1999) ("The lower courts . . . have held with virtual unanimity that a party cannot create a genuine issue of fact sufficient to survive summary judgment simply by contradicting his or her own previous sworn statement (by, say, filing a later affidavit that flatly contradicts that party's earlier sworn deposition) without explaining the contradiction or attempting to resolve the disparity."). Applera would have us agree with the district court that Dr. Sherman's declaration did not raise a genuine issue of material fact because he "offer[ed] no support, experimental, literary, or otherwise, for [his] assertion" that Kasai would substantially interfere, and that Applera is entitled to summary judgment of anticipation. See Summary Judgment, 2007 WL 2669025, at *13.

Applera's argument ignores the standard for summary judgment, which requires that Dr. Sherman's declaration be viewed in a light most favorable to Enzo. See Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp., 149 F.3d 1309, 1315 (Fed. Cir. 1998)

("In deciding whether summary judgment was appropriate, we view the evidence in a light most favorable to the party opposing the motion with doubts resolved in favor of the opponent.") (internal citations omitted). Viewing the declaration in a light most favorable to Enzo requires that Dr. Sherman's explanation be read as limited to the specific one-carbon aminomethyl group disclosed in Kasai and not as a sweeping condemnation of single bonds or an unyielding requirement of double bonds. See Sherman Decl. ¶ 44 ("[T]he aminomethyl group would not provide sufficient rigidity to prevent significant interference with hybridization.") (emphasis added). Dr. Sherman's statement that the aminomethyl group disclosed in Kasai would substantially interfere and Dr. Engelhardt's statement that a six-carbon diamine group would not are not inconsistent, particularly when viewed in a light most favorable to Enzo, as it must be.

Moreover, at least two characteristics of a linkage group contribute to its character as interfering with hybridization or not: the nature of the bonds (i.e., single or double) and the length of the chain. In his declaration, Dr. Sherman chose to focus on the first (the lack of a double bond) in explaining why Kasai would substantially interfere. The '824 patent indicates the preferability of a double bond in the linkage group. '824 patent col.8 ll.58-65 ("[I]t is generally preferred that the chemical linkage include an olefinic [(i.e., double)] bond . . . . [This] serves to hold the moiety A away from the base when the base is paired with another in the well known double-helix configuration."). See also Engelhardt Decl. Ex. A (seven of eight examples incorporate a double bond, including a short three-carbon chain linkage group). However, while Dr. Sherman did not discuss it, the '824 patent also recognizes that the length of the linkage group impacts hybridization and detection. See '824 patent col.8 ll.65-68 ("Moreover, single

bonds with greater rotational freedom may not always hold the moiety sufficiently apart from the helix to permit recognition by and complex formation with [a] polypeptide.") (emphasis added). It is elementary stereochemistry that a longer linkage group could hold the moiety farther from the hybridization site than a shorter one. Viewed with this understanding of the technology, the declaration of Dr. Engelhardt cannot be said to obviate the genuine issue of material fact raised by Dr. Sherman's declaration.

Applera also argues that because Kasai's $–CH_2–NH–$ linkage group is within the group of "even more preferred" embodiments, it cannot substantially interfere. However, there are an infinite variety of linkage groups "derived from a primary amine, [with] the structure $–CH_2–NH–$," see '824 patent col.9 ll.1-15, which suggests that not every "even more preferred" linkage group would satisfy the not substantially interfering element. Further, Enzo argues that the "even more preferred" language is properly read as describing a subset of the preferred embodiments—i.e., those with carbon-carbon double bonds at the α-positition—such that the most preferred embodiments have both a carbon-carbon double bond at the α-position, and are derived from a primary amine and include a $–CH_2–NH–$ group. The examples in the specification of the most preferred embodiment have both a carbon-carbon double bond at the α-position and an aminomethyl group. '824 patent col. 9 ll.8-16. Enzo's reading is reasonable, and should have been credited on summary judgment.

For the reasons stated, we reverse the district court's grant of summary judgment of invalidity of the asserted claims of the '824 and '767 patents as anticipated by Kasai.

2. Pingoud

Applera presents two arguments that Pingoud anticipates the '767 patent. First, it relies on a statement by its expert, Dr. Kricka, that "Pingoud was able to detect the label without apparent difficulty, so to the extent Enzo contends that the mere ability to detect a label is sufficient to satisfy this claim limitation presumably they would not dispute that Pingoud satisfies this claim limitation as well." Kricka Decl. ¶ 84, App. A at 60. Second, Applera repeats its argument that Pingoud belongs to the set of compounds described as "even more preferred" in the patents.

Neither argument is sufficient to sustain summary judgment. On its face, Pingoud notes that there was substantial interference with hybridization. Pingoud at 327 ("Codon-anticodon interaction . . . is severely affected by the [fluorescent labeling] modification."). "Codon-anticodon interaction" is indicative of hybridization, and "severely affected" suggests substantial interference. Dr. Sherman recognized this, and, unlike Dr. Kricka, opined that "there would be substantial interference" by the compound disclosed in Pingoud. Sherman Decl. at ¶¶ 61-62. Thus there is a genuine issue of material fact as to whether the Pingoud linkage group substantially interferes with hybridization.

We reject Applera's "most preferred embodiment" argument for the same reasons discussed above in regard to Kasai.

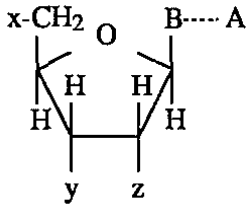
Therefore, we reverse the district court's grant of summary judgment of anticipation of the asserted claims of the '767 patent based on Pingoud.

3. Bauman

Enzo's argument with regard to Bauman is insufficient to raise a genuine issue of material fact. Bauman employs a mercury glutathione linkage group to attach moiety A

to base B. However, instead of attaching the linkage group before hybridization, Bauman first performs hybridization and then attaches the linkage group, along with moiety A, to the hybrid. Once attached, moiety A is detected by fluorescence. Because Bauman performs hybridization before labeling the polynucleotide, Enzo argues that Bauman cannot anticipate the asserted claims of the '928 patent. In Enzo's view, the claims "require that the linkage group not interfere after the label is attached." Reply Br. of Pl.-Appellants 23. We disagree.

First, the claims of the '928 patent are directed to a product, not a process. More specifically, independent claims 1 and 2 are simply directed to a "compound" having the structure:



It is irrelevant, for purposes of anticipation, what method is used, much less what order of steps is used, to attach both moiety A and the linkage group to base B. See In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985) ("The patentability of a product does not depend on its method of production.").

Second, as we have already explained, the "not interfering substantially" language in the '928 patent is silent as to hybridization. All that is required of this particular linkage group is that it not substantially interfere with the ability of A to be detected. Enzo does not dispute that Bauman discloses a linkage group that does not substantially interfere with the ability of A to be detected.

Because the district court correctly held that Enzo failed to raise a genuine issue of material fact with respect to Bauman, we affirm the judgment of anticipation as to claims 1 and 2 of the '928 patent.[5]

II. The '830 Patent

The district court construed the term "non-radioactive moiety" in the '830 patent to mean "a moiety that is utilized in indirect detection, i.e., a moiety that can be detected with a preformed detectable molecular complex." Claim Construction, 2006 WL 2927500, at *11. Enzo would like the term construed simply to mean "a non-radioactive detection moiety." Thus, under Enzo's proposed construction, the moiety could be utilized in either indirect detection (wherein the preformed detectable molecular complex is the thing that generates a detectable signal) or direct detection (wherein the non-radioactive moiety is itself the thing that generates a detectable signal). We agree with the district court's construction.

Claims 1, 12, and 18 are independent claims. Claim 14 is a multiple dependent claim that refers back to claims 1 and 12. The claims recite, with key term emphasized:

> 1. An oligo- or polynucleotide having at least one non-radioactive moiety directly or indirectly attached to each of the 5′ and 3′ end nucleotides thereof.
>
> 12. An oligo- or polynucleotide having at least one non-radioactive moiety directly or indirectly attached to each of the 5′ and 3′ terminal nucleotides external to a target hybridization region of said oligo- or polynucleotide.

[5] Because Bauman anticipates claims 1 and 2 of the '928 patent under the district court's narrower construction of moiety A, wherein A represents only a portion and not the entirety of the indicator molecule, Bauman would necessarily anticipate these claims if, as Enzo argues, A is broad enough to represent either a portion or the entirety of the indicator molecule. Because it would not change the result in this case, we decline to address Enzo's claim construction argument with regard to moiety A.

14. A nucleic acid hybridization assay composition comprising an oligo- or polynucleotide of claims 1 or 12, and a preformed detectable molecular complex.

18. A method for detecting a target nucleic acid sequence in a sample comprising:

rendering the nucleic acid in said sample in single-stranded form;

contacting said single-stranded nucleic acid under hybridizing conditions with (i) an oligo- or polynucleotide probe having at least one non-radioactive moiety directly or indirectly attached to each of the 5′ and 3′ end nucleotides thereof, said probe being capable of hybridizing to said target nucleic acid sequence, and (ii) a preformed detectable molecular complex; and

detecting any hybridized complexes, thereby detecting the target nucleic acid sequence.

Enzo concedes that the term "non-radioactive moiety" cannot be given its literal meaning (i.e., a molecular substructure not labeled with a radioisotope), since the claims would then encompass any piece of natural DNA, rendering the claims invalid on their face. The district court therefore looked to the specification, which contains no disclosure of direct detection but instead refers to an "analyte-specific moiety" detected using "detectable molecules." '830 patent col.3 ll.41-53. Because all detectable molecules mentioned in the specification are those relating to detection via a "preformed detectable molecular complex," the district court concluded that a "non-radioactive moiety" must be detected via a signal generated from the preformed detectable molecular complex rather than from the moiety itself. On appeal, Enzo faults the district court for equating "non-radioactive moiety" with "analyte-specific moiety," and argues that the specification instead equates "non-radioactive moiety" simply with "labeling" of nucleic acids using "labeling moieties." Id. col.1 ll.8-11. But even if a non-radioactive moiety is simply a "label," as Enzo suggests, this still leaves open the question whether

the non-radioactive moiety is itself capable of generating a detectable signal or whether the preformed detectable molecular complex is what generates the signal.

The claim language strongly suggests that the non-radioactive moiety serves simply as a binding site for a preformed detectable molecular complex, and that the signal is generated by the complex, not the moiety. Independent claim 18 is unambiguously limited to indirect detection via "a preformed detectable molecular complex." Id. col.14 ll.63-64. If the non-radioactive moiety were itself the thing that generated a detectable signal, then there would be no reason to contact it with the preformed detectable molecular complex, as required in part (ii) of the "contacting" step of claim 18. Moreover, in the last step of this claim, what is detected is "any hybridized complexes," not the moiety. Id. col.14 l.65 (emphasis added). Thus, at least with regard to claim 18, the "non-radioactive moiety" is a moiety that can be detected with a preformed detectable molecular complex. Enzo has not argued that the "non-radioactive moiety" should have a different meaning in independent claim 18 than in independent claims 1 and 12. Indeed, we have recognized that "claim terms are normally used consistently throughout the patent." Phillips v. AWH Corp., 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc).

Referring to the claim language, Enzo argues that the district court's construction of "non-radioactive moiety" violates the doctrine of claim differentiation. Under this doctrine, "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." Id. at 1315. Because dependent claim 14 adds "a preformed detectable molecular complex" to claim 1, Enzo asserts that the district court's construction of "non-

radioactive moiety"—which refers to detection with "a preformed detectable molecular complex"—renders the two claims coextensive. But the district court's construction imposes no requirement that a preformed detectable molecular complex is actually present in claim 1; rather, it simply requires the "non-radioactive moiety" to be capable of performing a function: "can be detected with a preformed detectable molecular complex." Claim Construction, 2006 WL 2927500, at *11 (emphasis added). Claim 1, unlike claim 14, is infringed even in the absence of a preformed detectable molecular complex. See Revolution Eyewear, Inc. v. Aspex Eyewear, Inc., 563 F.3d 1358, 1370 (Fed. Cir. 2009) (holding that a component of an accused device meets "capable of engaging" limitation even though device is not designed or sold with component in engaging configuration). Because claim 1 is broader than claim 14 under the district court's construction, this case simply does not implicate the doctrine of claim differentiation.

The specification lends no support to Enzo's proposed construction because it contains no disclosure whatsoever of direct detection. This fact alone is not dispositive, of course, because "it is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment—into the claims absent a clear indication in the intrinsic record that the patentee intended the claims to be so limited." Liebel-Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 913 (Fed. Cir. 2004). But, as already discussed, the claim language strongly suggests that the non-radioactive moiety must have the capability of being indirectly detected with a detectable molecular complex.

The prosecution history is not to the contrary. Enzo overcame an obviousness rejection by stating:

> Prior to the instantly claimed invention, no mention or suggestion was ever made regarding the attachment (directly or indirectly) of at least one non-radioactive moiety, e.g., biotin or a biotin analogue, to each of the 5′ and 3′ end nucleotides of an oligo- or polynucleotide. Furthermore, no prior art reference ever taught or suggested the possibility of a nucleic acid hybridization assay composition comprising such a labelled oligo- or polynucleotide and a preformed detectable complex, e.g., a preformed avidin or streptavidin detectable molecular complex, as defined by the present claims.

J.A. 307 (emphasis added). On appeal, Enzo argues that this statement supports its proposed construction because it equates a "non-radioactive moiety" with a "labeled oligo- or polynucleotide," which in turn suggests that the moiety is simply a "label." But again, the question is how this "label" is detected. The very same sentence that refers to the claimed compound as a "labelled oligo- or polynucleotide" also refers to a "preformed detectable complex," suggesting that detection is accomplished by the latter. Indeed, the unique binding of a biotin moiety with an avidin complex, referenced in this passage, is an example of indirect detection. Moreover, these prosecution statements were made with regard to all rejected claims standing or falling together, and were not directed to any dependent claim reciting a detectable molecular complex as an express limitation of the claim. All of this suggests that the non-radioactive moiety must be capable of indirect detection with a preformed detectable molecular complex. The prosecution history thus tends to undercut, rather than support, Enzo's proposed construction.

For the foregoing reasons, we affirm the district court's construction of "non-radioactive moiety." Because Enzo stipulated that it cannot prove infringement under this construction, we affirm the judgment of noninfringement of the '830 patent.

CONCLUSION

We reverse the district court's grant of summary judgment that the asserted claims of the '824 and '767 patents are invalid as indefinite and anticipated by Kasai and further that the asserted claims of the '767 patent are anticipated by Pingoud. We affirm the judgment that the '928 patent is invalid as anticipated. We affirm the judgment that the '830 patent is not infringed. The case is remanded for further proceedings consistent with this opinion.

AFFIRMED-IN-PART, REVERSED-IN-PART, and REMANDED