UNITED STATES DISTRICT COURT
DISTRICT OF CONNECTICUT

ENZO BIOCHEM, INC. ET AL.,	:	
Plaintiffs,	:	
	:	**No. 3:04cv929 (JBA)**
v.	:	
	:	
APPLERA CORP. ET AL.,	:	
Defendants.	:	

RULING ON DEFENDANT APPLERA'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY [DOC. # 181]

Plaintiffs Enzo Biochem, Inc., Enzo Life Sciences, Inc., and Yale University (collectively "Enzo") allege patent infringement under 35 U.S.C. §§ 271, et seq. against defendants Applera Corp. ("Applera") and Tropix Inc. ("Tropix") with respect to three of four "Ward Patents," specifically Claims 1, 18, 19, 21, 26, 28, 32, and 33 of U.S. Patent No. 5,328,824 ("'824 Patent"); Claims 1, 2, 8, 11, 13, 42, 46, 47, 48, 49, 50, 51, 67, 68, and 70 of Patent No. 5,449,767 ("'767 Patent"); and Claims 1 and 2 of Patent No. 5,476,928 ("'928 Patent"). (See Compl. [Doc. #1] at 1; Def. Reply Mem. [Doc. # 224] at 2 n.1.)[1] Defendant Applera now moves for summary judgment of invalidity as to these Ward patents on grounds of failure to satisfy the written description and enablement requirements of 35 U.S.C. § 112 ¶ 1, failure to

[1] Plaintiffs no longer press their claims related to Patent No. 4,711,955 ("'955 Patent").

satisfy the claim definiteness requirement of 35 U.S.C. § 112 ¶ 2, and anticipation under 35 U.S.C. § 102. For the reasons that follow, defendant Applera's Motion will be GRANTED.

I. Factual Background

As set out in the Court's Claim Construction Ruling, the Ward patents disclose a method of non-radioactive labeling for detecting the presence of DNA or RNA in a sample. See Enzo Biochem, Inc. v. Applera Corp., No. 3:04cv929 (JBA), 2006 U.S. Dist. LEXIS 74570 (D. Conn. Oct. 12, 2006) ("Claim Construction Ruling"). This method of labeling is effected via the formation of a complex between hybridized nucleotides and a detectable polypeptide. The Ward Patents, which share a specification, are based on a single application filed April 17, 1981 on behalf of then Yale professor Dr. David Ward and two colleagues. The first Ward Patent, the '955 Patent, see supra n. 1, issued in 1981; an overview of the asserted claims is provided below.

A. '824 Patent

The '824 Patent, which issued on July 12, 1994, discloses a two-step process by which a probe is hybridized with an analyte and then detected as a means of determining the existence of a

particular analyte in the sample. Of the asserted claims of this Patent, independent Claim 1 is representative:

> A method of detecting the presence or absence of a nucleic acid in a sample which comprises the steps of
> (a) contacting under hybridizable conditions said sample with at least one compound comprising the structure:
> [DIAGRAM]
> [....]
> wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing a detectable signal;
> wherein B and A are covalently attached directly or indirectly through a linkage group, 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;
> wherein if B is 7-deazapurine, A is attached to the 7-position thereof, and if B is pyrimidine, A is attached to the 5-position thereof;
> wherein m, n and p are integers, provided that m and p are not simultaneously 0 and provided further n is never 0; and
> wherein z represents H- or HO-; and
> (b) detecting said compound or compounds so as to detect said nucleic acid.

('824 Patent, Pls. Ex. 6.) Dependent Claims 18, 19, 21, 26, 28, 32, and 33 describe the structure of the A moiety, indicator molecule B, and the nucleic acid disclosed in Claim 1.

B. <u>'767 Patent</u>

The '767 Patent issued on September 12, 1995 and discloses a particular nucleotide useful in hybridization. Plaintiffs allege infringement of independent Claims 1, 42, and 48, and numerous

dependent claims. Claim 48 is representative:

> An oligo- or polynucleotide containing therein a sugar moiety having the structure: [DIAGRAM]
> [....]
> wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing a detectable signal; and
> wherein B and A are covalently attached directly or through 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, provided also that if B is a 7-deazapurine, A or the linkage group is attached to the 7-position of the deazapurine, and if B is pyrimidine, A or the linkage group is attached to the 5-position of the pyrimidine.

('767 Patent, Pls. Ex. 5.) Dependent claims 49, 50, 51, 67, 68, and 70 are directed to the structure of the sugar moiety or of A. Independent Claims 1 and 42 share much of the language in Claim 48, except that Claim 1 discloses that the oligo- or polynucleotide contains a "nucleotide" rather than a sugar moiety, and Claim 42 discloses an "oligo- or polynucleotide sequence comprising at least one of a moiety having the structure: -BA."

C. <u>'928 Patent</u>

Issued on December 19, 1995, the '928 Patent discloses a compound useful as a probe to detect the presence of and/or

localize specific polynucleotide sequences. Independent Claim 1 is representative:

> A compound useful as a probe for detecting the presence or absence of a nucleic acid, said compound having the structure: [DIAGRAM]
> [....]
> wherein 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;
> wherein B and A are covalently attached directly or through a linkage group, said linkage group not interfering substantially with detection of A;
> wherein if B is a purine, A is attached to the 8-position of the purine, if B is a 7-deazapurine, A is attached to the 7-position of the deazapurine, and if B is a pyrimidine, A is attached to the 5-position of the pyrimidine; and
> wherein each of x, y and z represents: [DIAGRAM].

('928 Patent, Pls. Ex. 4.) Independent Claim 2, the only other Claim asserted by Enzo, is substantially similar to Claim 1, except that it discloses that "one of x and y represents [DIAGRAM] and the other of x and y is absent or represents -OH or -H" and that "z represents H- or HO-."

The Court's Claim Construction Ruling construed certain terms relevant to the claims on the instant Motion. First, the '824 and '767 Patents were construed to "cover both direct and indirect detection," Enzo Biochem, 2006 U.S. Dist. LEXIS 74570 at 9, on the basis that "A comprises at least three carbon atoms and is one or more parts of a signaling moiety, which includes, in

some instances, the whole signaling moiety." Second, the terms "linkage group not interfering substantially with" and "linkage group that does not substantially interfere with" in all of the asserted independent claims were construed to mean that "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," id. at 16-17.

II. Summary Judgment and Invalidity Standards

Summary judgment is appropriate under Federal Rule of Civil Procedure 56(c) when the moving party establishes that there is no genuine issue of material fact to be resolved at trial and that the moving party is entitled to judgment as a matter of law. See Celotex Corp. v. Catrett, 477 U.S. 317 (1986). Materiality is determined by the substantive law that governs the case. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248 (1986). "Where the record taken as a whole could not lead a rational trier of fact to find for the nonmoving party, there is no genuine issue for trial." Matsushita Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 586 (1986).

"A defendant need not prove a negative when it moves for

summary judgment on an issue that the plaintiff must prove at trial. It need only point to an absence of proof on plaintiff's part, and, at that point, plaintiff must 'designate specific facts showing that there is a genuine issue for trial.'" Parker v. Sony Pictures Entm't, Inc., 260 F.3d 100, 111 (2d Cir. 2001), quoting Celotex, 477 U.S. at 324.

A patent is presumed valid, as are the individual claims of a patent. 35 U.S.C. § 282. The party claiming invalidity bears "the burden to show the invalidity of the claims by clear and convincing evidence as to underlying facts." Rockwell Int'l Corp. v. United States, 147 F.3d 1358, 1364 (Fed. Cir. 1998). This standard demands evidence that proves in the mind of the trier of fact "an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" Intel Corp. v. Int'l Trade Comm'n, 946 F.2d 821, 829-30 (Fed Cir. 1991) (affirming determination that patent not invalid where "extensive inference" from evidence did not meet the clear and convincing standard).

III. Discussion

A. Written Description Requirement

The first of defendant's summary judgment grounds is that Patents '824 and '767 are invalid under Patent Act § 112 ¶ 1,

which requires that a specification "contain a written description of the invention, and of the manner and process of making and using it, in . . . full, clear, concise, and exact terms," 35 U.S.C. § 112 ¶ 1. According to Applera, although Patents '824 and '767 have been construed by the Court to cover both direct and indirect detection, the specification inadequately describes a system for direct detection.

In order to satisfy the written description requirement, the specification must show that the applicant possessed the invention as of the filing date, Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991), thus ensuring that "the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification," Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345 (Fed. Cir. 2000). The written description may be accomplished "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed instruction." Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997). "While it is legitimate to amend claims or add claims to a patent application . . . there must be support for such amendments or additions in the originally filed application." PIN/NIP, Inc. v.

Platte Chem. Co., 304 F.3d 1235, 1247 (Fed. Cir. 2002). "The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." Capon v. Eshhar, 418 F.3d 1349, 1357 (Fed. Cir. 2005). A claim is not invalidated simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1366 (Fed. Cir. 2006).

In contesting whether the specification teaches direct detection, defendant makes several arguments. First, Applera focuses on the "A" moiety, which is defined in the specification as follows:

> A represents a moiety consisting of at least three carbon atoms which is capable of forming a detectable complex with a polypeptide when the compound is incorporated into a double-stranded ribonucleic acid, deoxyribonucleic acid duplex, or DNA-RNA hybrid;

'824 Patent 7:26-30.[2] Defendant contends that the specification discusses the "A" moiety as capable of only indirect detection, meaning that direct detection was not possessed by Enzo when the Ward Patents issued, and that the disclosed labels are described

[2] Because the specification is identical for all of the Ward Patents, the Court will cite only to the '824 Patent for consistency.

in reference to indirect detection.

Applera is correct that the specification repeatedly references "A"'s capability of "forming a detectable complex with a polypeptide ('824 Patent 3:49-50, 5:33-34, 7:26-27, 8:4-5, 11:16-17; 16:66-67), and describes "A" (in the form of disclosed labels biotin, iminobiotin, and various haptens) as "interacting with appropriate antibodies to produce complexes" (id. at 8:12-13) or as "coupled to potentially demonstrable indicator molecules" (including the fluorescent dyes fluorscein and rhodamine) to be used in detection of a biotin probe (id. at 18:7-17). According to defendant's expert Larry J. Kricka, "[t]he specification repeatedly and exclusively discloses that the 'A' moiety is detected not by itself, but by complexing it with a labeled (and thus detectable) polypeptide to form a complex that generates a detectable signal." (Kricka Decl. [Doc. # 183] ¶ 107.) He observes that "[e]ach disclosure in the specification of 'indicator molecules' explicitly describes such molecules as being coupled to a detector protein--an entity that is used to detect the 'A' moeity--and not to the 'A' moiety itself." (Id. ¶ 110.) Plaintiffs respond to these portions of the specification by arguing that because direct detection

methods using fluorescent dyes and other single-component signaling systems were known when the Ward specification was filed, the specification's disclosure of labeled nucleotides suitable for incorporation into polynucleotides is sufficient, and, more importantly, that Example 9 of the specification discloses direct detection.

While Examples 1 through 6 undisputedly disclose only indirect detection methods (Sinden Supplem. Expert Report, Pls. Ex. 3, ¶ 15), Enzo's expert witness Richard R. Sinden opines that Example 9, particularly in the context of Examples 7 and 8, "disclose[s] techniques that involve detection where A is the whole of the signalling moiety" (id. ¶ 10). Examples 7 and 8, entitled "Synthesis of NAGE-UTP and NAGE-dUTP," describe the method for synthesizing the linker arm NAGE, which can be attached to UTP and dUTP nucleotides. (Id. ¶ 11; '824 Patent at 28-29.) Example 9 sets out "Karyotyping," "Diagnosis of Genetic Disorders," and "Microorganism Detection and Identification" as "Uses of Labeled DNA Sequences." ('824 Patent at 29-30.) Sinden reads Example 9 as invoking the labeling procedures in Examples 7 and 8 and providing for direct detection methods using fluorescent dyes: he interprets the phrase "adding a fluorescent

stain to the label" in Example 9 as denoting attachment of a fluorescent dye to the available amine group of the NAGE linker from Examples 7 and 8, and not the addition of biotin with subsequent detection using a linked indicator as in indirect detection Examples 1 through 6. (Sinden Supplem. Expert Report, Pls. Ex. 3, ¶ 13.) Indirect detection using biotin as compatible with Examples 1 through 6 would lead to background interference or distort detection results, Sinden opines. (Id. ¶ 15.) Moreover, Sinden points to Example 9's allowance for "two sets of labels," a condition he claims is specific to the direct detection context. (Id. ¶ 16.)

Applera's expert Kricka, in contrast, claims that Example 9 simply elaborates on uses for labeled sequences set out in the preceding eight examples, all of which describe indirect detection methods. He quotes from the karyotyping section of Example 9, and reads it as exclusively describing indirect detection:

> polynucleotides are hybridized with chromosomal deoxyribonucleic acid and the resulting duplexes contact with appropriate polypeptides under suitable conditions to permit complex formation. The polypeptides include detectable moieties so that the location of the complexes can be determined and the location of specific genes thereby fixed.

Id. at ¶ 113, quoting '824 patent at 24:40-50. In addition,

Applera further points to a paper published by two of the Ward Patents' inventors, David Ward and Pennina R. Langer-Safer, in 1982 that discloses a method of performing the procedures in Example 9 using only indirect labels, as well as to a 1990 paper by Ward on using multiple probes labeled with different indirect labels to analyze chromosomes. See Pennina R. Langer-Safer, et al., "Immunological method for mapping genes on Drosophila polytene chromosomes," Proc. Natl. Acad. Sci. USA, (1982), Pls. Ex. 7; Ann L. Boyle, et al., "Differential distribution of long and short interspersed element sequences in the mouse genome: Chromosome karyotyping by fluorescence in situ hybridization," Proc. Natl. Acad. Sci. USA (1990), Pls. Ex. 8. Indeed, Sinden recognizes the two-color analysis method using indirect detection described in the 1990 paper as "one embodiment" of what is contemplated by Example 9 such that "it is possible to carry out the procedures of Example 9 of the Ward patent using an indirect detection system." Apr. 13, 2006 Sinden Dep., Def. Ex. 9, at 127, 128.)[3]

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[3] That the prosecution histories of the '824 and '767 Patents reveal "A" moieties disclosing only biotin and iminobiotin, indirectly detectable moieties, does not necessarily compel a finding that the patents fail to meet the written description requirement with respect to direct detection, particularly given that the letter defendant sent to the U.S. Patent and Trademark Office ("PTO") protesting issuance of the '767 Patent could be

In Univ. of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916 (Fed. Cir. 2004), the Federal Circuit affirmed a judgment of invalidity for inadequate written description where the functional description of the invention consisted of a bare assertion that the patent covered "'a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product,'" id. at 928, without further narrowing its scope by disclosing "just which peptides, polynucleotides, and small organic molecules have the desired characteristic of selectively inhibiting PGHS-2," id. at 927 (internal quotations omitted)(emphasis in original). The court found that the language of the specification had cast too wide a net, cautioning that while patent applicants need not provide a step-by-step narrative of reduction to practice, an ordinarily skilled artisan cannot be left with "a vague functional description" which does not fairly delineate the infringing from the non-infringing, id. at 926, 927. See also

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interpreted as reflecting Applera's understanding that the '767 and '824 Patents cover direct detection. (See Letter from Applera's Senior Patent Counsel Stephen C. Macevicz to Assistant Commissioner of Patents Lawrence J. Goffney, Jr., Pls. Ex. 20, at GT008336 ("Nothing in any of the Ward specifications, the prosecution up to 1994, or pending claims up to 1994 give any indication that the invention includes compounds covering DNA sequencing fragments. . . . The only rationale for this claim is to obtain a claim that literally covers DNA sequencing fragments so that the opportunistic patent priorietor can extract royalties or other concessions out of the real industry participants under threats of patent infringement suits.").)

Lizardtech, Inc. v. Regents of the Univ. of Cal., 424 F.3d 1336, 1346 (Fed. Cir. 2005) (affirming judgment of invalidity where patent specification recited the procedure by which to manufacture one possible invention purported to be covered by the patent, but where specification was impermissibly vague as to the range of inventions covered thereby).

The facts at bar do not present the Court with such a clear want of specificity. While the text of the specification, which repeatedly discusses the "A" moiety as "forming a detectable complex with a polypeptide, suggests disclosure of only indirect detection, the record contains clashing but reasonable expert interpretations of the meaning of Example 9. Thus, the Court concludes that defendant has not proven by clear and convincing evidence that a skilled practitioner would read the '824 and '767 Patents to disclose <u>only</u> indirect detection, and summary judgment on this point is inappropriate.

B. <u>Enablement</u>

Next, defendants claim that Ward Patents '824 and '767 are invalid for lack of enablement under Patent Act § 112 ¶ 1, which requires the specification's language to include "such full, clear, concise, and exact terms as to enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and use the [invention]." Applera notes that in an unrelated interference proceeding before the U.S. Patent and Trademark Office ("PTO") on May 3, 2007, concerning a patent outside this case being disputed by Enzo and Applera,[4] Enzo's expert Dr. Bruce A. Roe submitted a declaration asserting that direct labeling was not enabled in any scientific publication until 1985. Since the Ward Patents were available before 1985, including European Patent No. 063879 - the European equivalent of the Ward Patents, which was published on November 3, 1982, Ward Eur. Pat. App., Def. Supplem. Ex. 3, - Applera argues that Dr. Roe's opinion amounts to an admission by Enzo that the Ward patents do not enable the direct detection method, and that because the specification does not allow practice of the full scope of the claimed invention without undue experimentation, the Ward Patents are invalid for lack of enablement. Enzo accuses defendants of mischaracterizing Roe's testimony, which they claim pertained only to whether a specific labeling chemistry was actually disclosed in a particular patent, and point out that Roe admitted that he had not exhaustively searched the prior art before testifying.

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[4] Specifically, patent 5,821,058 ('058 patent), and allowed patent application 08/486,069.

The interference proceeding in which Roe's declaration was submitted was an inter partes PTO administrative proceeding to determine which of multiple entities first invented specific subject matter claimed in competing patents or patent applications. See 35 U.S.C. § 135. Claim 14 of the disputed '058 Patent, which is assigned to the California Institute of Technology and exclusively licensed to Applera, sets out a method of DNA sequencing in which polynucleotide fragments are "tagged with a chromophore or fluorophore," that chromophore or fluorophore being a directly detectable label. (Roe Decl., Def. Supplem. Ex. 2, ¶ 21, quoting '058 Patent.) On May 3, 2007, Enzo moved that Caltech be denied the '058 patent's claimed "priority date" of January 16, 1984 on the grounds that the application on which Caltech bases its priority (No. 06/570,973 ("'973 Application")) lacks an enabled embodiment of Claim 14 of the '058 patent, because: "Methods for tagging nucleotides with fluorescent labels to determine the sequence of a polynucleotide were not publicly known until at least 1985." (Enzo Subst. Mot. in Interf. Procdg. 4, Def. Supplem. Ex. 1, at 4.)

In his declaration, Roe opines that a person skilled in the art, prior to 1985, "would not have been able to select the precise reagents, reaction conditions and process steps necessary

to achieve a successful coupling of a chromophore or fluorophore from the multitude of possibilities, without at least undue experimentation." (Roe Decl., Def. Supplem. Ex. 2 ¶ 28.) In writing his declaration, Roe "reviewed the scientific literature published from about the late 1970s to about the late 1980s, in the field of DNA sequencing." (Id. ¶ 29.) At his deposition, Roe testified that his review of the literature before writing his report included "at least the Langer et al., that's David Ward I think is on that. I'd have to check." (June 12, 2007 Roe Dep., Def. Supplem. Ex. 4, at 116.)[5] When queried about the methods enabled by the plaintiffs' `955 patent, Roe was unsure until given a chance to re-read the patent:

> Q: Let me be more specific, is there anything in this Ward patent that you could point me to that would tell a skilled person how to couple a fluorophore directly to a polynucleotide?
>
> A: Can I take some time to look through the patent?
>
> [....]
>
> Q: Just to confirm, you've had the chance to look through the Ward `955 patent?

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[5] With respect to the Langer-Safer/Ward publication that Roe had reviewed (Langer-Safer (1981), see supra) on "enzymatic synthesis of biotin-labeled polynucleotides" (June 12, 2007 Roe Dep., Def. Supplem. Ex. 4, at 116-17), Enzo argues that Kricka's knowledge of this article is irrelevant because it disclosed no example of direct labeling, in contrast to Examples 7, 8, and 9 of the Ward Patents specification. As the same arguments are made here regarding the Examples as in relation to the lack of written description, supra, the Court will not restate its analysis.

A: Yes, I have.

Q: And is there anything in that patent that would teach a person of skill how to directly couple a fluorophore to a polynucleotide? And let me just be clear, when I say directly, I mean by a covalent bond whether through a linker arm or not.

A: No. Thank you for giving me time to look through that.

(Id. at 133.) Dr. Roe certified the accuracy of the deposition transcript, and did not submit any amendments or corrections.

The key inquiry is the extent to which the subject matter of Roe's testimony ("coupling a fluorophore or chromophore to the 5' amino of a polynucleotide fragment in a manner suitable for determining the sequence of the polynucleotide" (Roe Decl., Pls. Supplem. Opp. Ex. 2, ¶ 26)) constitutes direct detection and hybridization. If the coupling testified to by Roe signifies direct detection and hybridization, then Roe's testimony can be taken to mean that detection and hybridization were not enabled before 1985.

In the Court's view, the question of the breadth of Roe's testimony is resolved by his clarification that his interference declaration merely states that "certain coupling chemistry was not known before a certain date" (id. at 26) (emphasis added), and that the declaration itself addresses the '973 Application

and the "aliphatic amino group at the 5' terminus" (Roe Decl., Pls. Ex. 2, ¶¶ 25, 26, 30, 35, 38). A later declaration by Roe in the same proceeding confirms the conclusion that Roe's denial of enablement in the Ward patents is limited to a particular procedure not at issue in this litigation:

> All the steps for conducting DNA sequencing were known to a person of skill in the art in 1982 except for the step of tagging a polynucleotide fragment with a chromophore or fluorophore in a manner suitable for determining the polynucleotide sequence from the fragments in accordance with the Count.

(Roe Second Decl., Def. Supplem. Reply Ex. 1, ¶ 60.) Moreover, Enzo rightly points out that Applera's own expert Kricka testified and stated in his report on invalidity that direct labeling was known in the field by the time the first Ward patent issued in 1981 (Kricka Expert Report, Pls. Ex. 8, ¶ 30; Kricka Dep., Pls. Ex. 9, at 170), with which assessment Enzo's experts Sinden and Sherman agreed (Sinden Reply Expert Report, Pls. Ex. 7 ¶ 56; Sinden Dep., Pls. Ex. 6, at 46; Sherman Dep., Pls. Ex. 5, at 110). However, as Applera notes, the experts agreed that attachment of fluorescent labels for hybridization was known in 1981, not that the specific method suitable for DNA sequencing was known. (Def. Supplem. Reply at 8.)[6]

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[6] Plaintiffs also point out that Applera's anticipation argument, see infra, is itself premised on the notion that direct labeling

As the declaration of Roe is focused on what was known about direct detection in relation to 5' amino coupling in the '058 Patent/'093 Application context, the evidence proffered in support of defendant's enablement ground for invalidity does not compel granting summary judgment.

C. Claim definiteness

Applera argues that the Ward Patents are invalid because the term "interfering substantially" does not meet the definiteness requirement of Patent Act § 112 ¶ 2, which demands that patent claims "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention," 35 U.S.C. § 112 ¶ 2, as understood by one skilled in the art, Invitrogen Corp. v. Biocrest Mfg., 424 F.3d 1374, 1383 (Fed. Cir. 2005). The exact words employed in a patent specification are vital, as "claims delineate the scope of the invention using language that adequately notifies the public of the patentee's right to exclude." Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1347 (Fed. Cir. 2005). A claim will be rejected for

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of nucleic acids was known before 1981. See Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research, 346 F.3d 1051, 1054 (Fed. Cir. 2003) (A patent claim "cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.").

indefiniteness where it "is not sufficiently precise to provide competitors with an accurate determination of the 'metes and bounds' of protection involved." Ex parte Lyell, 17 U.S.P.Q.2d 1548, 1550-51 (Bd. Pat. App. & Int. 1990). A specification invites a determination of indefiniteness when it "leaves those skilled in the art entirely without guidance" as to the scope of requirement, Exxon Research and Eng'g Co. v. United States, 265 F.3d 1371, 1379 (Fed. Cir. 2001), adrift without the "objective anchor" which makes a term definite, Datamize, 417 F.3d at 1350. Where, as here, the term in question expresses a measure of degree, "the district court must determine whether the patent's specification provides some standard for measuring that degree." Seattle Box Co. v. Indus. Crating & Packing, Inc., 731 F.2d 818, 826 (Fed. Cir. 1984). For understandable reasons of fundamental fairness to others practicing the art, the presence or absence of a standard "cannot depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention." Datamize, 417 F.3d at 1350.

The terms "not interfering substantially" and "does not substantially interfere" appear in Claims 1, 42, and 48 of the '767 Patent; Claim 1 of the '824 Patent; and Claims 1 and 2 of the '928 Patent. In Claim 1 of the '824 patent, the term appears as follows: "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." The Court's Claim Construction Ruling read this to mean that "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." Enzo Biochem, 2006 U.S. Dist. LEXIS 74570 at 17.

Defendant contends that a person of skill in the art would not be able to determine from the specification how to measure "interference" in the context of "hybridization" and "detection."[7] Defendant also urges that the specification fails to provide guidance as to how to assess whether "interference" is present, since the significance of nucleotide alteration may vary according to the length of a polynucleotide (i.e., the alteration of a single nucleotide would affect hybridization more profoundly on a shorter chain than on a longer one).

For its part, Enzo argues that this Court construed the term during the claim construction phase, and is therefore prevented

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[7] Plaintiffs emphasize that words of degree like "substantially" are not per se indefinite, see, e.g., Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1575-76 (Fed. Cir. 1986) ("so dimensioned"); BJ Servs. Co. v. Halliburton Energy Servs., Inc., 338 F.3d 1368, 1372-73 (Fed. Cir. 2003) ("about"), but this contention misses the mark of Applera's argument, which is specific to whether the claims at issue sufficiently define the meaning of "not interfering substantially" and "does not substantially interfere."

from finding the term indefinite, citing two recent decisions from the Federal Circuit, Energizer Holdings, Inc. v. Int'l Trade Comm'n, 435 F.3d 1366, 1371 (Fed. Cir. 2006) (noting that "[a] claim that is amenable to construction is not invalid on the ground of indefiniteness") and Aero Prods. Int'l, Inc. v. Intex Recreation Corp., 466 F.3d 1000, 1016 (Fed. Cir. 2006) (stating the corollary, that "if a claim is not amenable to construction, the claim is invalid as indefinite under 35 U.S.C. § 112, ¶ 2").

However, in both Aero Products and Energizer, the trial court had assigned precise definitions to the terms at issue during the claim construction phase. In Energizer, the dispute centered on the phrase "said zinc anode," and the narrow question of whether the phrase properly referred to a specific antecedent term, 435 F.3d at 1368-1369. In Aero Products, the Federal Circuit weighed the definiteness of the phrase "complete hermetic seal," which the trial court had construed as meaning "a seal that does not require any additional parts to retain nearly or largely all of the air in the bed," 466 F.3d at 1008. The district court struck this compromise between two very specific construction proposals – the plaintiff's "seal that does not require any additional parts to retain 'nearly' or 'largely' all of the air in the bed such that the bed maintains its desired

firmness for the expected duration of use," and the defendant's terser "nearly or largely impervious to air," id.

Here, the parties have presented this Court not with specificity, but with an adverbial phrase which, when added by the plaintiff as an amendment to the original patent in 1986,[8] was presumably meant to distinguish the Ward method of detection and hybridization from other methods which did cause substantial interference. At construction, neither party proposed a concrete definition for "substantial interference" expressed in signal-to-noise ratios, temperature, time, or any other laboratory metric which a practitioner could use as a milepost when performing hybridization and detection. Enzo proposed that the term be taken to mean, recursively, "not rendering impractical or overly difficult," Pl.'s Cl. Constr. Memo [Doc. # 89] at 23. Applera, meanwhile, proposed that the term be read as effectively meaning that the binding procedure function transparently, such that:

> that the ability of A (when attached to B via said linkage group) to form a detectable complex is essentially identical to the ability of A to form a detectable complex when directly attached to B.

Def.'s Cl. Constr. Memo [Doc. #91-2] at 22-23. Beyond that, the parties' arguments on both construction and definiteness of the

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[8] Supplemental Amendment application dated Mar. 21, 1986 reproduced at defendant's memo in support of summary judgment on invalidity [Doc. # 185], Ex. 23.

key phrase has been comparatively sparse, with defendants reserving argument on construction of "substantial interference" in the interest of arguing for indefiniteness at summary judgment,[9] and plaintiffs' reply construction brief not even listing "substantial interference" as an area of dispute.[10] Faced with the parties' two alternative meanings of "substantial interference," this Court chose to use the term to limn the behavior of the linkage group, but could not affix a more precise technical definition.[11]

Defendant's expert Kricka states in his report that "[t]he term 'not interfering substantially' in the context of 'hybridization' and/or 'detection' does not appear anywhere in the specification outside of the claims," and thus "provides no guidance to allow one skilled in the art to measure 'interference' in the context of 'hybridization' and 'detection.'" (Kricka Decl. ¶ 129.) Kricka further states that "there is no guidance in the specification for one to determine

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[9] Defs.' Cl. Constr. Br. at 22.

[10] See Pl. Reply Cl. Constr. Br. [Doc. # 98] at i.

[11] The Court ruled that "substantial interference" will be taken as meaning that "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 [the A moiety] to be detected. Enzo Biochem, Inc. v. Applera, Inc., 2006 U.S. Dist. LEXIS 74570 at 16.

how to assess if there was any 'interference'" at all, given that "[w]hile a very minor alteration of a single nucleotide in a chain of three nucleotides would have a profound effect on the ability of that oligonucleotide to hybridize, the same modification on a longer oligonucleotide, such as one having 50 or 100 nucleotides, might not have any effect on hybridization." (Id. ¶ 130.) Defendant notes that Enzo's Vice President Dr. Dean Engelhardt testified that he did not know how one should measure the attribute of not substantially interfering. (Jan. 16, 2007 Engelhardt Dep., Def. Ex 25, at 128-29.) Similarly, Enzo's Vice President of Clinical Affairs, Dr. Barbara Thalenfeld, when asked how she would "measure whether only the linkage group does or does not interfere with hybridization" or "if the linkage group itself was interfering with the ability of the reporter to be detected," responded "I don't know." (Thalenfeld Dep., Def. Reply Ex. 6, at 178-79.)

The plaintiffs, relying upon the opinion of expert Sinden, argue that the term is sufficiently definite. Sinden opined that "substantial interference" is "clear and plain language" which denotes the point at which [something] will "prevent you from getting the experiment to work." (Apr. 13, 2006 Sinden Dep., Pls. Opp. Ex. 11, at 138:11-15). Sinden's report observes that the term means that "the linkage group may interfere with

hybridization and detection so long as the interference is not substantial, i.e., an amount that would render hybridization or detection impractical or overly difficult." (Sinden Report, Pls. Ex. 17, at 29). He also explained at his deposition how temperature affects DNA hybridization and that a linker arm that altered the melting temperature of particular DNA would bear on "substantial interference." (Apr. 13, 2006 Sinden Dep., Pls. Opp. Ex. 11, at 134-36.)[12]

While arguing that the approach of the point of failure ("impractical or overly difficult"), is measurable in terms of "degrees of interference" (Apr. 13, 2006 Sinden Dep., Pls. Opp. Ex. 11, at 139:2-3), when pressed to identify the precise point at which interference ripens to substantiality, Sinden stated:

> It's probably in the hands of the experimenter. Clearly, if it didn't work at all, it wouldn't work. If it worked 50 percent and you were able to get your signal and publish a paper, you may go with it.

(Id. at 139:8-12.) Moreover, Sinden concedes that inasmuch as his report equates substantial interference with the point at

[12] For his part, Kricka admits that "melting temperature of modified polynucleotides could conceivably be one measure of the effect of a linker arm on hybridization." (Kricka Decl. ¶ 129, citing Claim Construction Ruling at *16.) Even though Kricka and Sinden agree that melting temperature could have an effect on hybridization, plaintiffs have not pointed to anything in the patents instructing a person of skill in the art on how to determine substantiality of interference based upon melting temperature of polynucleotides.

which hybridization or detection becomes overly difficult, "[o]verly difficult may mean different things to different people." (Apr. 13, 2006 Sinden Dep., Def. Ex. 9, at 139-40.) Sinden's testimony would thus seem to corroborate Kricka's view that the face of the patent's specification provides no standalone gauge of "substantial interference," but rather requires experimentation in order to determine where the claims set forth in the Patents become useful. Left to Sinden's interpretation, the Patent claims would cover any interactions which succeed, but not those which do not - rendering "substantial" a nullity. Moreover, it is instructive that neither Thalenfeld nor Engelhardt, both scientists and Enzo executives, could conjecture a means of determining substantiality of interference.

As this Court understands that allegations of indefiniteness may not be rebutted merely by the unrestrained, subjective opinion of the inventor, the claims must fail. In Datamize, the Federal Circuit affirmed a finding of indefiniteness where a patent specification purported to cover the creation of "aesthetically pleasing" elements in a computer graphical user interface. The deficiency in such a term, the Court found, was that Datamize had "offered no objective definition identifying a

standard for determining when an interface screen is 'aesthetically pleasing,'" Datamize, 417 F.3d at 1342, but instead simply provided the testimony of an expert who listed elements of design which would lead one skilled in the art to deem a given user interface "aesthetically pleasing." The Court found that an expert's list of elements or indices alone "fails to explain how the parameters should be evaluated or weighed to reach the conclusion" that a given creation meets the patent's subjective standard. Id. at 1354, see also Honeywell Int'l, Inc. v. Int'l Trade Comm'n, 341 F.3d 1332, 1339 (Fed. Cir. 2003) (affirming judgment of invalidity where the proper temperature at which a crucial step in the manufacturing-process invention was to take place was provided only by the testimony of patent holder's expert).

The Federal Circuit's treatment of indefiniteness in Exxon also informs this Court's decision. The two patents at issue in that case covered "improvements in what is known as the Fischer-Tropsch process for converting natural gas to liquid hydrocarbon products," Exxon, 265 F.3d at 1373, which, if implemented, would "increase[] the relative catalyst productivity in the Fischer-Tropsch reaction by at least 30%" and "optimally operat[e] a slurry bubble column . . . to produce hydrocarbon products at an increased rate." Id. at 1374. While the trial court had

determined that four of Exxon's claims were indefinite for indefiniteness, the Federal Circuit reversed. Three of those claims centered on numerical terms,[13] but the analysis of most interest here is the Federal Circuit's treatment of a term which was not expressed within a mathematical formula, "substantial absence of slug flow."[14] In the district court, defendants had argued that gauging the substantiality of slug flow was not possible given that the specification did not set forth the proper means by which slug flow was to be measured. The Federal Circuit found the term to be sufficiently definite when read within the context of the entire patent, i.e. a system by which to increase efficiency of the Fischer-Topsch reaction by at least 30%. Because the patent specification taught that slug flow interferes with the efficient completion of the patented method, the Court held that the substantial absence of slug flow "can be determined with reference to whether reactor efficiency is

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[13] See Exxon Research and Eng'q, 265 F.3d at 1377 (deeming "to increase substantially" sufficiently definite where patent specification defines such an increase in catalyst activity as being between between 30-75%), id. at 1378 (holding "for a period sufficient" to be definite where the patent specification set out a minimum time period for sufficiency, but not a maximum time), id. at 1382 (finding that specification that particles be of an "average diameter" set forth in a mathematical formula acceptably definite).

[14] Apparently referring to the movement of large gas bubbles through the reactor.

materially affected," as measured by identifiable data points such as mass transfer performance. Exxon, 265 F.3d 1380-1381. Thus, by measuring the efficiency of their reactions - the innovation claimed by Exxon - practitioners could determine whether or not a particular procedure infringed upon Exxon's patent.

By contrast, the Ward patents do not set forth improvements upon a known process, but rather, describe a new procedure of non-radioactive detection and hybridization which does not cause "substantial interference" with a successful result. The specifications neither set forth how one would gauge substantial interference, nor delimit the threshold at which interference with the procedure prevents Ward's method from being implemented. As plaintiff's expert Sinden frankly admitted, substantial interference has thus been left to the experimenter to determine the conditions under which detection and hybridization either succeeds or fails. Although the patent expresses a term of degree ("substantial interference"), expert testimony has shown the term to be an illusory yardstick which, if permitted to stand, would sweep all successful hybridization and detection into the ambit of the patents' coverage, while excluding any unsuccessful procedures. This effect would be entirely unlike Exxon's patents, which covered only those Fischer-Tropsch

reactions which were made observably more efficient by use of the patented methods. It cannot be the case that a term added as a limiting clarification to the Ward patents can now be used to amplify the patents' coverage.

In sum, plaintiff has been caught in one of patent law's traps: having used language in its patent application which stakes out the zone of exclusivity for its invention, the plaintiff must now be able to show that its language is nonetheless definite enough to put others skilled in the art on notice of what has been patented. Because defendant has proven by clear and convincing evidence that the term "interfering substantially" in Claim 1 of the '824 Patent; Claims 1, 42, and 48 of the '767 Patent; and Claims 1 and 2 of the '928 Patent is indefinite, summary judgment of invalidity for indefiniteness is granted on these patent claims.

D. Anticipation

Although the indefiniteness of the claims at issue is fatal, thoroughness counsels addressing all of the parties' remaining arguments. As a third ground of invalidity, defendant asserts that the '824, '767, and '928 patents were anticipated by three prior art references published before April 17, 1981 (the date that the original Ward patent application was filed): a journal

article by Alfred Pingoud, et al. published in 1977; a journal article by Hiroshi Kasai, et al. published in 1979; and a doctoral thesis by J.G.J. Bauman published in 1980. (See Alfred Pingoud, et al., "Fluoresceinylthiocarbamyl-tRNA: a useful Derivative of tRNA (E.coli) for Physiochemical Studies," Nucleic Acids Res. (1977) ("Pingoud"), Def. Ex. 27; Hiroshi Kasai, et al., "Specific Fluorescent Labeling of 7-(aminomethyl)-7-deazaguanosine Located in the Anticodon of tRNA Isolated from E. Coli Mutant," Nucleic Acids Res. (1979) ("Kasai"), Def. Ex. 28; J.G.J. Bauman, "Cytochemical Detection of Specific Nucleic Acid Sequences Development and Application of In Situ Hybridisation Methods for Fluorescence Microscopy" (doctoral dissertation) (1980) ("Bauman"), Def. Ex. 29.) Specifically, Applera contends that Kasai anticipates the '767 and '824 Patents; Pingoud anticipates the '767 and '928 Patents; and Bauman anticipates all three patents. Plaintiffs argue that none of the three publications discloses every claim asserted as construed by the Court and that a genuine issue of material fact exists as to whether the articles are enabling references that qualify as "prior art."[15]

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[15] The Court disposes briefly of Sherman's general attack on the three references for failing to meet "the standard that an organic chemist in the early 1980's would have used in order to

Whether a patent claim is anticipated under 35 U.S.C. § 102 is a question of fact requiring element-by-element evaluation of the disclosure of the claims in the prior art reference, as "each and every limitation . . . either expressly or inherently" must be disclosed, Bristol-Myers Squibb Co. v. Ben Venue Labs. Inc., 246 F.3d 1368, 1374 (Fed. Cir. 2001). "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." Elan Pharms., Inc., 346 F.3d at 1054 (internal quotation marks

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determine whether or not a new organic molecule had been synthesized" and as thus being non-enabling (Sherman Decl. ¶ 33). Without citation to any authority, Sherman conclusorily states that a publication "lacking a sufficient number of [10] criteria" would not be considered to provide necessary disclosure to enable one of skill in the art to make and use a new chemical substance, and thus that Kasai and Pingoud in particular should be rejected as prior-art references because they are not enabling. (Id.) Sherman's proffered rubric, however, is unsubstantiated and thus rejected as a general argument against defendant's anticipation claims. Moreover, as defendant points out, Kasai and Pingoud were in any case published in the journal Nucleic Acids Research; and for a reference to be enabling, "all that need be shown is that one of skill in the art could make the disclosed compounds," not that it was actually made. (Def. Reply Mem. at 7-8, citing In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985) ("[E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. . . . It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.").) See Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368 (affirming partial denial of summary judgment of invalidity for anticipation where anticipatory experiment "enabled the performance of [antitumor drug administration] steps even though [it] did not achieve a favorable outcome").

and citation omitted).

1. Kasai

Kasai "describes a procedure for fluorescent labeling of E. coli preQ1-containing $tRNA^{Tyr}$ with dansyl chloride." (Kasai, Def. Ex. 28, at 232.) The article reports that "[t]he modified $tRNA^{Tyr}$ was found to be active both in amino-acylation and in binding to ribosomes" and that "this fluorescent probe should be useful for conformational studies on tRNA." (Id.) Defendant argues that Kasai discloses a labeled polynucleotide sequence (dansyl-tRNA) that meets each limitation of the relevant claims of the '767 and '824 Patents.

a. '767 Patent

To illustrate what it alleges to be the anticipation of the '767 patent, Applera focuses on the sugar moiety-containing oligo-/polynucleotide of Claim 48, arguing that Kasai's tRNA compound includes -CH2-NH-, the aminomethyl linkage group whose structure is "preferred" in the Ward Patents specification, which constitutes Claim 8 of the '767 Patent and Claim 16 of the '928 Patent. Defendant claims that Kasai's tRNA compound hybridizes with complementary polynucleotides and

becomes detectable via measurement of the fluorescence of the dansyl moiety, Kasai Fig. 2, Def. Ex. 28, at 235 - thus, because hybridization and detection are made possible in this fashion, that Kasai meets the "not substantially interfere" limitation. Although this Court has determined that the "substantially interfere" language in the Ward Patents is the basis for their invalidity, interpretation of the phrase for purposes of anticipation does not affect the invalidity ruling.

Enzo's expert Sherman disputes the satisfaction of the "not substantially interfere" limitation by stating that the aminomethyl group serving as a linker arm in the compound "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.) However, as defendant notes, Sherman offers no support, experimental, literary, or otherwise, for this assertion. In addition, implicit in Sherman's observation about the aminomethyl-group linker is a definition of substantial or

significant interference as allowing for hybridization, which conflicts with Sinden's interpretation of the term "not substantially interfere" as "it can't prevent you from getting the experiment to work." See Apr. 13, 2006 Sinden Dep., Def. Ex. 9, at 138.

A general retort made by plaintiffs is that Kasai cannot be anticipatory because it is directed to naturally substituted bases, viz. preQ1, which Enzo contends is "specifically excluded from the Ward Patent claims." (Sherman Decl. ¶ 42.) Enzo cites the specification, which reads that "7-deazapurines useful in this invention must not be naturally substituted at the 5- or 7-positions, respectively." ('824 Patent at 7:64-67.) Defendant responds that Sherman relies on the specification rather than the patent claims, impermissibly importing limitations into the claims for purposes of avoiding prior art. See Phillips v. AWH Corp., 415 F.3d 1303, 1323 (Fed. Cir. 2005). Moreover, Applera claims that the phrase from the specification is quoted out of context and in fact "refers to the fact that the Ward patents' described methods for adding linkage groups to the 5-position of pyrimidines and the 7-position of 7-deazapurines will not work if there is already a carbon-carbon bonded substituent at these positions such as in thymine, 5-methylcytosine, and 5-

hydroxymethylcytosine," i.e., that "modified bases derived from bases lacking natural substitutions at the 5- or 7- positions 'are more readily prepared or used or both, and therefore are presently preferred.'" (Kricka Reply Decl. ¶ 8, citing '824 Patent at 7:53-57.) Kricka opines that "Kasai discloses how to synthesize 7-(aminomethyl)-7-deazaguanosine and react this compound with dansyl chloride. . . . Therefore, one of skill in the art could make an 'unnaturally' substituted 7-deazapurine and label it with a fluorescent dye if they wished." (Id. ¶ 11.) The Court agrees that the Ward Patent claims do not contain a specific limitation which excludes all naturally-occurring linkage groups (modified 7-deazapurine bases), and thus, a finding that Kasai anticipates the '767 Patent is not precluded. Defendant has met its burden of proving Kasai's anticipation of each limitation of every asserted claim of the '767 Patent.

b. '824 Patent

The arguments with respect to Kasai's alleged anticipation of the '824 Patent, including the non-naturally occurring argument, are basically identical to those above for the '767 Patent. The '824-specific arguments are addressed here.

Kasai discloses that "binding of danyslated Tyr-$tRNA^{Tyr}_{preQ1}$ to E. coli ribosomes was stimulated by template, poly(U,A,C)." (Kasai, Def. Ex. 28, at 236.) According to Kricka this

anticipates Claim 1's method for detecting nucleic acids (poly(U,A,C) or poly(U,C) containing ribosomal RNA) that hybridize or bind with the dansyl-labeled polynucleotide $tRNA^{Tyr}$. (Kricka Decl. ¶ 68-76; Kasai, Def. Ex. 28, at 236-38.) Sherman disputes this by asserting that the tRNA in Kasai is used for "conformational characterization," not detection of nucleic acids, and does not disclose hybridization between two complementary polynucleotides, but between a polynucleotide and a stimulated ribosome. (Sherman Decl. ¶¶ 51-53.) However, Kricka explains that the ribosomal RNA of E. coli used in Kasai is referenced as a type of polynucleotide in the '824 Patent ('824 Patent at 17:24), and thus that when the "tRNA binds to a ribosome, portions of the tRNA hybridize to portions of the ribosomal RNA at various stages in the translation process. At the same time, the anticodon portion of the tRNA hybridizes with codon portions of another polynucleotide" (Kricka Reply Decl. ¶ 29). Indeed, Kasai notes that "[b]inding of [^{14}C]Tyr-tRNA to E. coli ribosomes in the presence of polynucleotide template was carried out as reported by Nishimura et al." (Kasai, Def. Ex. 28, at 233), indicating that tRNA-ribosome bonding was an established form of polynucleotide hybridization. As plaintiffs fail to rebut defendant's proof of anticipation, and for the reasons

stated above with respect to the '767 Patent, the Court finds that defendant has proven by clear and convincing evidence that Kasai anticipates every claim of the '824 Patent.

2. Pingoud

Pingoud describes the labeling at "uncommon base Q" – which had recently been identified when Pingoud was published and was later supplanted in Kasai by the preQ1 nucleoside – of the modified tRNA polynucleotide "FTC-$tRNA^{Tyr}$," and shows to what extent the modification affects the biological activity of the tRNA. (Pingoud, Def. Ex. 27.) Applera contends that Pingoud is an anticipatory reference as to the '767 and '928 Patents.

a. '767 Patent

Defendant contends that Pingoud discloses the labeled polynucleotide FTC-$(QU)_p$, whose structure is described in the claims of the '767 patent. The structural identity of the nucleotides is substantially undisputed, except that plaintiffs again make the same argument as with Kasai that apropos the linkage group, the "does not substantially interfere" limitation is unmet, and that the "naturally substituted" limitation is implicit in the claim--the same arguments made with respect to

anticipation based on Kasai. For the same reasons these arguments were rejected supra, the Court rejects them here, and the Court has in any case concluded that Patent '767 is invalid for anticipation by Kasai.

b. '928 Patent

Kricka opines that Claims 1 and 2 of the '928 patent were disclosed by Pingoud. As to Claim 1, Applera reads Pingoud as disclosing a fluorescein labeled 7-deazaguanosine nucleoside that is "[a] compound useful as a probe for detecting the presence or absence of a nucleic acid" to either detect the presence of $tRNA^{Tyr}$ when the nucleoside is incorporated into the polynucleotide, or by digesting the polynucleotides to individual nucleosides and then detecting the disclosed labeled nucleoside. As to Claim 2, defendant makes the same arguments for the terms of that claim which are identical to that of Claim 1 and adds that the labeled polynucleotide FTC-$(QU)_p$ is useful as a probe to detect $tRNA^{Tyr}$.

The locus of debate with respect to the '928 Patent concerns the "A" moiety in Claims 1 and 2, which "represents at least three carbon and an indicator molecule," and intersects with the question of whether both indirect and direct detection are disclosed by the Patent. As the Court determined supra that

Applera has failed to meet its burden of proving invalidity for lack of written description as to direct detection, the Court evaluates whether Pingoud is anticipatory as to both indirect and direct detection. The parties agree that in order to have anticipated the '928 Patent, Pingoud's "A" moiety must consist of a fluorescein dye indicator molecule and another portion containing at least three carbon atoms. Defendant argues that "the fluoresceinylthiocarbamyl moiety [in Pingoud] is split into two components: a portion of the fluorescein dye that can independently act as a fluorescent dye and another portion containing at least three carbons." (Def. Mem. at 39.) Enzo contests that the moiety can really be "split," and points to Kricka's testimony "that one of skill in the art would not consider breaking up fluorescent molecules into their constituents." (Kricka Reply Decl. ¶ 33; Kricka Decl. in Supp. of Def. Mot. for Summ. J. of Non-Infr., Pls. Ex. 25 ¶¶ 30, 31.) Although Kricka defends his comment as responsive to Sinden's "advocat[ing] breaking single fluorescent dyes into constituent parts" (id.), Sinden's testimony was directed to splitting a compound consisting of a fluorescein donor dye attached to a rhodamine acceptor dye, i.e., the structure of defendant's allegedly infringing compounds. (Sinden Decl. in Supp. of Pls.'

Opp. to Def. Mot. of Summ. J. of Non-Infr., Pls. Ex. 24, ¶¶ 29-31.)

As the party claiming invalidity, defendant's burden is high: Applera must prove invalidity by "clear and convincing evidence as to underlying facts," Rockwell Int'l Corp., 147 F.3d at 1364. Here, the combination of Kricka's disavowal that one would split fluorescent dyes like that in the Pingoud moiety, taken together with defendant's failure to show that Sinden's discussion of splitting applied outside the context of Applera's fluorescein-rhodamine compound, prevents this Court from concluding that Pingoud's moiety meets the three-carbon-plus-indicator-molecule limitation in the '928 Patent, and thus defendant's Motion of invalidity for anticipation based on Pingoud is denied with respect to '928 Patent Claims 1 and 2.

3. Bauman

The third article claimed to be prior art is a doctoral thesis written by Dutch scientist J.G.J. Bauman, which was publicly available more than one year prior to the filing of the original Ward patent.[16] Chapter 8 of Bauman's thesis sets forth

[16] Enzo's concern about the non-disclosure of the full Bauman reference was cured by submission of the entire dissertation and accompanying documents with Applera's reply memorandum.

a method of indirect detection involving the incorporation of pyrimidine nucleotides labeled with a Hg-Glutathione-Trinitrophenyl ("TNP") hapten and fluorescent antibodies to TNP. Defendant claims that Bauman shows that the hapten-labeled polynucleotide can be used as a probe in a hybridization assay to detect the presence of nucleic acids in a sample, and is thus an anticipatory reference of the three Ward Patents.[17]

The parties make generalized arguments not specific to the particular claims. First, the parties dispute whether the mercury-glutathione linker (the mercury bonds are the C-Hg bond between A and B and the Hg-S bonds in A) in Bauman is usable for typical hybridization experiments. Bauman explains that under certain conditions there were "[p]roblems observed in hybridising mercurated polynucleotides." (Bauman, Def. Ex. 29, at 161.) However, it notes that "[t]he loss of mercury during the hybridisation as a result of the thermal instability of the -C-Hg-bond (Dale and Ward, 1975) can be avoided by using low tempoeratures and formamide containing buffers." (Id. at 162.) According to Applera, this remedial prescription makes the Bauman

[17] Sherman argues that Claim 21 of the '824 Patent and Claim 70 of the '767 Patent should not be deemed asserted as anticipated by Bauman because they are not specifically addressed in Kricka's chart illustrating the anticipation claimed. (Sherman Decl. ¶¶ 66, 67.) However, these claims are in fact addressed in that chart. (See Kricka Decl. App. A. at 18, 32.)

compound usable in hybridization, and plaintiffs offer no evidence to rebut this, except to cite one sentence of the Ward Patents specification,[18] Sherman Decl. ¶ 72. However, this section of the specification does not address mercury, and Sherman does not explain how this bears on the analysis. Thus, the inaptness of mercuriated polynucleotides for hybridization does not dispose of the anticipation argument.

Second, Enzo and Applera disagree as to whether the mercury ligand in Bauman substantially interferes with hybridization. The indirect detection method in Bauman begins with RNA "mercurated by incubation in mercuric acetate," but at the next step, "[t]he acetate ligand of the mercuri-nucleotides is replaced by the CN^- ion, in order to facilitate hybridisation." (Bauman, Def. Ex. 29, at 142-43.) That this alteration is required, plaintiffs argue, signifies that "the glutathione linkage group interferes with hybridization" (Sherman Decl. ¶ 74). Moreover, Enzo points out that Bauman uses the synthetic homopolymer poly(U) in its experiments, which plaintiffs claim "provides an increased incidence of hybridization allowing for a greater amount of interference to occur without resulting in

[18] '824 Patent at 6:64-68 reads: "[T]he physical and biochemical properties of polynucleotides containing small numbers of probe substituents should not be significantly altered so that current procedures using radioactive hybridization probes need not be extensively modified."

failure of hybridization," Sherman Decl. ¶ 76. However, in addition to Sherman's failure to support his statement that use of Poly(U) results in increased hybridization and thus greater interference, Applera correctly points out that the Ward Patents do not preclude use of unnatural homopolymers; in fact, the specification itself states, "Another embodiment of this invention involves detection of poly A-containing sequences using poly U" ('824 Patent at 24: 51-54). Thus, the Bauman references satisfy the "not substantially interfering" limitation in the Ward Patents.

The third aspect bearing on whether Bauman is anticipatory stems from the Court's construction of the Ward Patents as disclosing both direct and indirect detection. The claim language "wherein the moiety A comprises an indicator molecule" and "wherein A comprises an indicator molecule" from the '767 and '824 Patents, was interpreted in the Court's Claim Construction Ruling interpreted to mean "that A may be a part of or the entire signaling moiety." Enzo, 2006 U.S. Dist. LEXIS at 11-12. In no uncertain terms, the Court concluded at claim construction that "the plain language and structure of the '824 and '767 Patents indicate that these patents cover both direct and indirect detection." Id. at 9. While the parties agree that Bauman does

not address direct detection, Applera argues that it need not include both direct and indirect detection to be anticipatory. However, the caselaw is clear that in order for a reference to be anticipatory, it must "disclose every limitation of the claimed invention, either explicitly or inherently," Liebel-Flarsheim Co., 481 F.3d at 1381, and as Bauman only discloses indirect detection, it is not an anticipatory reference rendering Patents '767 and '824 invalid. Summary judgment of invalidity for anticipation is thus denied based on Bauman as regards the '767 and '824 Patents.

Lastly, with respect to the '928 Patent, in addition to the earlier discussion of whether B meets the "not substantially interfering" limitation, plaintiffs' expert Sherman applies the same reasoning discussed above with respect to non-disclosure of direct detection to argue against anticipation. However, as diagrammed in defense expert Kricka's comparative chart, the three-carbon-plus-indicator-molecule structure is supported by the compound set out in Bauman: the complex consisting of the Hg-Glutathione-TNP, the rabbit TNP-antibody, and the swine antibody to the rabbit antibody. Kricka Decl. App. A at 83-84. As the other limitations are also diagrammed and well supported by defendant's expert, plaintiffs' brief retort is insufficient to

rebut the evidence presented that '928 Patent Claims 1 and 2 are anticipated by Bauman. Summary judgment is granted on grounds of anticipation with respect to the '928 Patent.

III. Conclusion

Accordingly, the Court concludes that the Claims 1, 2, 8, 11, 13, 42, 46, 47, 48, 49, 50, 51, 67, 68, 70 of the '767 Patent; Claims 1, 18, 19, 21, 26, 28, 32, 33 of the '824 Patent; and Claims 1 and 2 of the '928 Patent are invalid based on anticipation by prior art. Defendant Applera's Motion for Summary Judgment of Invalidity [Doc. # 181] is therefore granted. The Clerk is directed to close this case.

IT IS SO ORDERED.

/s/

JANET BOND ARTERTON, U.S.D.J.

Dated at New Haven, Connecticut, this 6th day of September, 2007.