United States District Court,
D. Connecticut.

ENZO BIOCHEM, INC., Enzo Life Sciences, Inc. and Yale University,
Plaintiffs.
v.
APPLERA CORP. and Tropix, Inc,
Defendants.

Civil No. 3:04cv929

Oct. 12, 2006.

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CLAIM CONSTRUCTION RULING

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Plaintiffs in this case allege that defendants infringed six patents issued between 1987 and 1995, including the four "Ward patents," U.S. Patent Nos. 4,711,955 ('955 patent), 5,328,824 ('824 patent), 5,449,767 ('767 patent) and 5,476,928 ('928 patent), the "Brakel patent," No. 5,082,830 ('830 patent), and the "Stavrianopoulos patent," No. 4,994,373 ('373 patent).

The patents cover various techniques and processes for detecting the presence of a particular strand of nucleic acids (*i.e.,* DNA or RNA) in a sample. The Ward patents disclose the invention of non-radioactive labeling and specify formation of a complex between the hybridized FN1 nucleotides and a detectable polypeptide. Thus, for instance, the ' 824 patent discloses a two-step process, whereby a probe FN2 is hybridized with an analyte,FN3 and then the probe is detected as a means of determining the existence of a particular analyte in the sample. The invention disclosed in the ' 373 patent is the method of the prior Ward patents, but with the additional issue of whether it is the analyte or probe that attaches to a solid support (such as a glass test tube), washed with the test sample to see if they will create a hybrid pair, and then detected by the label attached to the probe.

FN1. "Hybridization" is defined as "the binding of two separate, complementary strands of nucleic acids to form nucleic acid hybrids." See Defs.' Opening Claim Construction Br. [Doc. # 91-1] at 11 (drawing on

Expert Report of Larry Kricka, Def. Ex. 10 and 11).

FN2. A "probe" is "a short DNA sequence of a know[n] sequence," id. at 12.

FN3. An "analyte" or "target" is an "unknown nucleic acid," id.

The '830 Brakel patent discloses the use of multiple copies of a non-radioactive detectable signal on both the 3' and 5' ends of the probe to increase detection. The '955 Stavrianopoulos patent, the parties agree, covers an indirect detection method wherein the probe is labeled with biotin (vitamin B12) or a variant, which non-covalently binds to avidin or streptavidin (egg white protein), which in turn is labeled with a detectable probe.

There are four principal areas of dispute between the parties: whether the ' 824, '767 and '928 Ward patents cover both direct and indirect identification systems, or only indirect systems; whether "non-radioactive moiety" in the '830 patent means any detectable moiety or only an indirectly detectable one; whether "polynucleotide" in the '373 patent refers to any multiple-nucleotide molecule or only the "analyte" in the sample; and whether "soluble signal" in the '373 patent includes light.

I. Standard

The construction of patent claims is a matter of law within the exclusive province of the Court. *See Markman v. Westview Instruments, Inc.,* 517. U.S. 370 (1996). In construing patent claims, the words of a claim are typically "given their ordinary and customary meaning," *see e.g.,* Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996), which meaning has been interpreted as "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." Phillips v. AWH Corp., 415 F.3d 1303, 1313 (Fed.Cir.2005). Claim construction, therefore, "begins with the claims themselves, the written description, and, if in evidence, the prosecution history." Microsoft Corp. v. Multi-Tech Sys., Inc., 357 F.3d 1340, 1346 (Fed.Cir.2004).

As *Phillips* clarified, in determining the meaning given to a claim term by a person of ordinary skill in the art, that person "is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." Phillips, 415 F.3d at 1313 (also stating "[t]he best source for understanding a technical term is the specification from which it arose, informed, as needed, by the prosecution history," id. at 1315 (citing cases)). The specification "is the single best guide to the meaning of a disputed term." *Id.* at 1315. *Phillips* warns, however, that courts should "avoid importing limitations from the specification into the claims." *Id.* at 1323.

Additionally, a court may consider the prosecution history as intrinsic evidence of the meaning of a disputed term. "Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent." Phillips, 415 F.3d at 1317.

When the proper claim construction is not "readily apparent" from the claim term and other intrinsic evidence, a court may look to "sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean." Id. at 1314. There is no "magic formula" to claim

construction, and a court is "[not] barred from considering any particular sources or required to analyze sources in any specific sequence, so long as those sources are not used to contradict claim meaning that is unambiguous in light of the intrinsic evidence." Id. at 1324.

II. Ward Patents

A. '*767 and* '824 Patents*, Claim 1: "A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing a detectable signal" and "signalling moiety"*

The '767 and '824 patents claim: "A method of detecting the presence or absence of a nucleic acid in 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...." '824 Pat. 30:49-31:29. Plaintiffs construe this term such that *A* may constitute, in some instances, the whole signaling moiety (a chemical entity) capable of direct and indirect detection. See Expert Report of Richard Sinden, Def. Ex. 12, at 25 ("I understand the claims of the '824 and ' 767 Patents as requiring that the A moiety (i) have at least three carbon atoms and (ii) form one or more parts of a signalling moiety capable of producing a detectable signal.").

Plaintiffs argue that "at least one component" can mean "from one to all of the component parts of the signalling moiety," because scientists recognize the existence of single-component systems. (See Pls.' Claim Constr. Mem. at 16.) Further, they point out that dependent Claims 67, 68 and 70 of the '767 patent and Claims 18, 19 and 21 of the '824 patent specifically provide that " *A* comprises an indicator molecule," FN4 and argue that it would be impermissible to construe the independent claim more narrowly than the dependent claims.

FN4. '767 Patent, Claim 67: "An oligo-or polynucleotide of claim 1 or 48 wherein A comprises an indicator molecule."

'767 Patent, Claim 68: "An oligo-or polynucleotide of claim 67 wherein said indicator molecule is fluorescent, electron dense, or an enzyme capable or depositing insoluble reaction products."

'767 Patent, Claim 70: "An oligo-or polynucleotide of claim 68 wherein fluorescent indicator molecule is selected from the group consisting of fluorescein and rhodamine."

'824 Patent, Claim 18: "The method of claim 1 wherein the moiety *A* comprises an indicator molecule."

'824 Patent, Claim 19: "The method of claim 18 wherein said indicator molecule is fluorescent, electron dense, or is an enzyme capable of depositing insoluble reaction products."

'824 Patent, Claim 21: "The method of claim 19 wherein fluorescent indicator molecule is selected from the group consisting of fluorescein and rhodamine."
Additionally, plaintiff's expert, Dr. Richard R. Sinden, testified at the Markman hearing that the specification includes an example of direct detection. Examples 1-6 of the patents describe indirect detection, where

biotin or iminobiotin is complexed with detectable polypeptide, and Examples 7 and 8 merely suggest the use of a NAGE linker arm between the nucleic acid and *A,* which was well known in the art. However, Example 9 describes use of successive chemical reactions, involving covalent bonds, that would only function using direct detection with fluorescent labels.

Defendants construe Claim 1 as precluding the possibility of *A* being the whole signalling moiety. They primarily rely on the specification, which states several times in each patent that " *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" DNA or RNA. Defendants argue that because this specification does not teach a directly detectable moiety, Claim 1 must not do so. Defendants also argue that because the specification states that *A* is "formed," *A* must have multiple components and cannot itself be the directly detectable complex. Additionally, they rely on competing dictionary definitions that differ from plaintiffs', as well as that the six articulated "essential criteria" for *A* listed in the specifications, which, they argue, require that, among other properties, *A* be able to "react specifically with chemical or biological reagents to provide a sensitive detection system," '824 Pat. 6:35-37, and that the "detection system" be able to react with *A,* '824 Pat. 6:55-57, suggesting that *A* itself is not directly detectable.

The Court finds that the plain language and structure of the '824 and '767 Patents indicate that these patents cover both direct and indirect detection. Plaintiffs acknowledge that dependent claims 2-11 of the '824 Patent, and dependent claims 3, 54-59 and 61 of the '767 Patent, teach indirect detection. They teach that *A* is a "ligand" that is capable of binding with a detectable polypeptide, and therefore that *A* is not itself detectable. However, another chain of dependent claims in each patent teaches direct detection, with " *A* compris[ing] an indicator molecule." '767 Patent, Claims 67, 68, 70; '824 Patent, Claims 18, 19, 21; *see also supra* note 4.

"[T]he 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." Philips, 415 F.3d at 1315. Thus, the presence of dependent claims in both patents that teach both direct and indirect detection creates a presumption that Claim 1, the independent claim, is not limited to either. The specifications do not alter this conclusion. While "claims must be read in view of the specification," Philips, 415 F.3d at 1315, and the specification is "[t]he best source for understanding a technical term," *id.,* courts are also to "avoid importing limitations from the specification into the claims ." Id. at 1323. It is true that in the two Ward patents at issue, the specifications largely focus on indirect detection. However, the expert evidence indicates that Example 9 could involve direct detection. *See* Reply Expert Report of Richard R. Sinden, Def. Ex. 13, para.para. 56, 57 (citing Kricka Report, Def. Ex. 10, para. 30). Thus, importing into Claim 1 only the examples of indirect detection from the specification would skew the full illustrative range of all examples, resulting in utilization of the specifications as "limitations" on Claim 1 rather than as aids for understanding technical terms.

Defendants argue that the term "comprise" in the dependent claims asserted to teach direct detection implies that the indicator molecule is only a part of a multi-component system. The dependent claims, however, utilize "is" and "comprises" interchangeably. For example, Claim 67 of the '767 Patent teaches that " *A comprises* an indicator molecule," and Claims 68 and 70 teach that "An oligo-or polynucleotide of claim 67 wherein said indicator molecule *is* fluorescent, electron dense, or an enzyme capable or depositing insoluble reaction products," or " *is* selected from the group consisting of fluorescein and rhodamine." The drafting of this claim language is less than clear, but in the context of all the dependent claims taken together, the Court sees no basis for inferring from the word "comprise" in certain claims that *A must* have more than one component, as opposed to suggesting that *A may* have more than one component. *See infra* s. I.F.

The Court therefore finds that *A* may be a part of or the entire signalling moiety. For this reason, it declines to limit Claim 1 only to indirect detection, and adopts plaintiffs' construction of the disputed Claim 1 language in the '824 and '767 Patents: " *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."

Accordingly, the Court also construes the term "signalling moiety," as including, but not limited to, "a chemical entity capable of producing a detectable signal."

B. '928 Patent, ***Claim 1: A moiety is "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 '928 patent utilizes a different definition of "signalling moiety" from that in patents '767 and '824. Claim 1 of that patent reads: "... 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." (emphasis supplied). Despite the differences from the '767 and '824 Claim 1 language, plaintiffs construe this Claim in the same fashion as the comparable claims in the '767 and '824 patents, namely, that the *A* moiety can be the entire indicator molecule.

Plaintiffs support the view that Claim 1 of the '928 patent should be construed the same as the '767 and '824 patents by pointing to the abstracts and specifications of all three patents which contain the same definition of *A* ("... wherein *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" DNA or RNA).

Nonetheless, the Claim 1 language of the '928 patent is clearly different from the two earlier patents. Rather than saying A "represents" the indicator molecule described, it states that A has "at least three carbon atoms *and* " the indicator molecule. The plain language therefore precludes a construction where *A* is the entire molecule.

Accordingly, the Court adopts defendants' construction of Claim 1 of the ' 928 patent, such 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."

C. '928 Patent, '824 Patent, '955 Patent, ***Claim 1: "Said Linkage Group Not Interfering Substantially With"*** **/** '767 Patent, ***Claim 1: "Linkage Group That Does Not Substantially Interfere With"***

All four of the Ward patents claim a linkage group "not interfering substantially with" or "that does not substantially interfere with" detection of *A*. The linkage group at issue is between *A* and *B,* where *A* is defined above and *B* is defined in all three patents as either purine, 7-deazapurine or pyrimidine that attaches to a nucleotide.

Plaintiffs construe this language to mean that the linkage group "cannot substantially interfere with the characteristic ability of the compound or [nucleic acid] sequence to hybridize with a nucleic acid and cannot substantially interfere with formation of the signalling moiety or detection of the detectable signal. This means that the linkage group *may interfere with both hybridization and detection so long as the interference*

is not substantial ..." Sinden Report at 29 (emphasis added).

Defendants argue that the term "substantially" means 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. Claim Constr. Br. [Doc. # 91] at 22-23. They draw this language from a description of the invention, which states that the modified polynucleotides claimed are capable of denaturation and renaturation at melting point temperatures "essentially identical to that of the control, biotin-free DNAs." '824 Pat. 18:66. Plaintiffs' expert, Dr. Sinden, testified that melting point is related to interference with hybridization. Sinden Dep. at 136. However, he never adopted the "essentially identical" definition. Instead, he stated that the definition of "substantial" is "difficult to answer" and "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. Defendants offered no expert testimony commenting on this term or rebutting plaintiffs' expert testimony, and the language from the specification concerning melting points appears to be taken out of context and not relevant to the claims in question.

The more likely, and more persuasive, root for the claim term "not interfering substantially" is the explanation in the detailed description that the detection uses a "linker arm" between *A* and *B* to allow for hybridization:

[T]he detection system should be capable of interacting with probe substituents incorporated into both single-stranded and double-stranded polynucleotides in order to be compatible with nucleic acid hybridization methodologies. To satisfy this criterion, it is preferable that the probe moiety be attached to the purine or pyrimidine through a chemical linkage or "linker arm" so that it can readily interact with antibodies, other detector proteins, or chemical reagents.

'824 Pat. 6:55-63.

Thus, the claim language should be construed to account for the function of the linker arm. As plaintiffs request, the terms "not interfering substantially with" and "that does not substantially interfere with" detection of *A* will be 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." Nothing in the specification or preferred embodiments supports the narrower construction urged by defendants.

D. '824 Patent, ***Claim 1(b): "Detecting Said Compound or Compounds so as to Detect Said Nucleic Acid"***

Claim 1 of the '824 Patent discloses two steps to the claimed method for detecting the compound that includes the signaling moiety: (a) hybridizing the nucleic acid sample to the specified compounds; (b) "detecting said compound or compounds so as to detect said nucleic acid." '824 Pat. 31:42-43. Plaintiffs argue that this terminology means that the compounds which are detected do not necessarily have to remain hybridized to the nucleic acid in order to permit detection of the nucleic acid. They base their argument on the fact that dependent claim 24 claims a "method of claim 1 wherein said detecting step (b) is carried out when the compound is hybridized to the nucleic acid," '824 Pat. 32:51-53. Where a dependent claim contains this kind of limitation, it is "presum[ed] that the limitation in question is not present in the independent claim," see Philips, 415 F.3d at 1315 (citing Liebel-Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 910 (Fed.Cir .2004)), because if it were present in the independent claim, the dependent claim would be

redundant, *see* id. at 1324-25.

Defendants construe the claim language at issue to mean "detecting said compound or compounds *hybridized to said nucleic acid sample* " so as to detect said nucleic acid. In other words, they argue the patent does not cover detection of the probe after it has been separated from the sample.

The specification, however, is not limited to methods of detection only while the DNA duplex is hybridized. The specification states that its "general scheme illustrates only procedures used for gene mapping (cytogenetics), and recombinant DNA-technologies," *i.e.,* for purposes of "detecting and/or localizing specific polynucleotide sequences...." '824 Pat. 19:22-23, 61-63. The specification states that the invention may also be useful for diagnosing infections ("bacterial, fungus, virus, yeast, or mammal" or drug resistant organisms), *i.e.* where the scientist does not need to know the sequence of the polynucleotides, merely that polynucleotides from an infectious organism are present. For the latter purpose, the specification states,

... a polynucleotide is prepared which is complementary to the nucleic acid sequence which characterizes the organism or its antibiotic resistance and which additionally includes one or more modified nucleotides according to this invention. This polynucleotide is hybridized with nucleic acid obtained from the organism under scrutiny. Failure to hybridize indicates absence of the organism or of the resistance characteristic. *Hybridized nucleic acid duplexes* are then identified by forming a complex between the duplex and a suitable polypeptide which carries a detectable moiety, and detecting the presence of the complex using an appropriate detection technique. Positive detection indicates that the complex, *the duplex* and therefore the nucleic acid se [q]uence of interest are present.

'824 Pat. 20:24-38 (emphases added). Contrary to defendants' argument, it does not appear that this aspect of the specification was intended to describe the method's application to "gene mapping" and "recombinant DNA technologies," which were the primary intended use. Rather, the description quoted above, including its reference to "hybridized nucleic acid duplexes" being detected, are limited to the diagnostic examples.

Further, as plaintiffs argue, Claim 24 claims a method where the "detecting step ... is carried out when the compound is hybridized to the nucleic acid." Again, drawing on the dependent-independent claim logic in *Phillips,* supra at 14, because the dependent claim contains this limitation, the independent claim is presumed not to include it. Philips, 415 F.3d at 1315.

For these reasons, the Court adopts plaintiffs' construction of "detecting said compound or compounds so as to detect said nucleic acid" to mean that the compounds which are detected do not necessarily have to remain hybridized to the nucleic acid in order to permit detection of the nucleic acid.

E. '928 Patent, ***Claim 1: "Compound Useful as a Probe "***

Defendants construe "probe" to mean a "hybridization probe, *i.e.,* a labeled portion of DNA used in a hybridization assay." They distinguish between an "indicator probe," which they define as the *A* moiety that is detected by the scientist, and a "hybridization probe," meaning the strands of DNA and RNA that hybridize with the sample, and which have indicators attached to them. *See* Kricka Rebuttal Report at 8. They argue that in the context of the '928 patent, "probe" refers to a "hybridization probe" because the claims and diagrams show that the indicator probe *A* is attached to a nucleotide, and the patent claims "the entire disclosed nucleotide." However, defendants also state that the '928 specification utilizes the term "probe" in both the sense of an indicator probe and a hybridization probe. Defendants also concede that in

the other Ward patents "probe" can designate both indicator probes and hybridization probes.

Plaintiffs define "probe" to mean "a compound for detecting and/or localizing specific polynucleotide sequences." Pl. Mem. of Law [Doc. # 89] at 24. They argue that the term "probe" is not limited by the claim language to a single class of probes, such as those used in a hybridization assay. Further, they argue that the specification does not limit the invention to hybridization probes because it only states that the claimed compounds " *may* be used as probes in biomedical research, clinical diagnosis, and recombinant DNA technology," ' 928 Pat. 5:60-62 (emphasis added), and "are widely useful as probes in biomedical research and recombinant DNA technology." Id. 7:55-56.

The '928 Patent refers to biotin as a probe, which defendants acknowledge suggests an indicator probe. '928 Pat. at 13:54, 13:65-66, 18:6, 18:13. For example, the specification refers to "biotin nucleotides" that may be introduced into growing polynucleotides in order to detect the growing polynucleotide chains; it also teaches that "enzymes can be used as reagents for introducing probes such as biotin into highly selective or site-specific locations in polynucleotides...." Id. at 13:59-67. As plaintiffs argued at the Markman hearing, there are numerous non-hybridization uses for biotin nucleotides, including DNA sequencing.

Because the specification teaches biotin nucleotides and not nucleotide sequences as probes, the probes in the patent are not limited to "hybridization probes." Defendants' limitation on Claim 1 that the "compound useful as a probe" must be a "hybridization probe" finds no support either in the language of Claim 1 or the specification. For these reasons the Court adopts plaintiffs' construction that "a compound useful as a probe" means "a compound for detecting and/or localizing specific polynucleotide sequences."

F. '928 Patent, ***Claims 1 and 2, and*** '955 Patent, ***Claim 5: "Compound Having the Structure"***

Claim 5 of the '955 Patent claims "[a] compound having the structure ..." according to a particular diagram. Claim 1 of the '928 Patent also claims a "compound useful as a probe for detecting the presence or absence of a nucleic acid, said compound having the [same] structure."

Plaintiffs would construe the phrase "having the structure" identically to the phrase "comprising the structure," including " *any* compound having the recited structure," even if the compound also has additional elements to those recited. Pl. Mem. of Law [Doc. # 89] at 27 (emphasis added). Defendants argue that "comprising" and "having" have different meanings depending on the context, and specifically that the inventors used "comprising" in an open sense and in conjunction with those signaling moieties that could have additional elements, but used "having the structure" where the structure was set and could not have additional elements. See discussion supra at 9. For instance, Claim 1 of the '955 patent claims a "nucleotide or oligo- or polynucleotide sequence comprising at least one of a moiety having the structure ...," and Claim 9 of that patent uses the same language.

According to the Federal Circuit,

When a patent claim uses the word "comprising" as its transitional phrase, the use of "comprising" creates a presumption that the body of the claim is open. In the parlance of patent law, the transition "comprising" creates a presumption that the recited elements are only a part of the device, that the claim does not exclude additional, unrecited elements.

The transition "having" can also make a claim open. However, the term "having" does not convey the open-

ended meaning as strongly as "comprising." "Having," for instance, does not create a presumption that the body of the claim is open.

Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l., 246 F.3d 1336, 1348 (Fed.Cir.2001); *see also* Lampi Corp. v. American Power Products, Inc., 228 F.3d 1365, 1376 (Fed.Cir.2000) ("Transitional phrases such as ... 'having' ... must be interpreted in light of the specification to determine whether open or closed language is intended.").

Here, the Court agrees with the parties that no assistance can be found in the specification. However, the claim language, and particularly the evident differences in the inventors' use of "having" and "comprising," lead to the conclusion that "having" is meant to be a closed term in the context of the ' 955 and '928 Patents. Specifically, the inventors signaled that they intended the term "comprising" to be open by language indicating that more than one moiety could "comprise" the claimed sequence or compound: "comprising *at least one* of a moiety ...," '955 Pat. 31:35; 32:54-55, or "comprising a detectable polypeptide *complexed with* a compound...." '928 Pat. 31:26-27, 32:19-20 (emphases added). By contrast, they did not modify the term "having," which is always stated in the form, "a compound having the structure...." *See, e.g.,* '955 Pat. 31:35, 31:68, 32:55, '928 Pat. 30:5, 30:49.FN5

FN5. Defendants' argument that open bonds, shown by "-," indicate an open claim element is not entirely persuasive. While this does appear to be the case in the '955 Patent, where Claims 9 and 15 use the word "comprising" and also indicate open bonds in the diagrams, in Claims 3 and 6 of the '928 Patent, which use the term "comprising," diagrams without open bonds are used. The better evidence, therefore, comes from the claim language itself, not the diagrams.

Accordingly, in the context of these patents, the Court construes the term "having" to be intended by the inventors to be a closed term precluding additional elements, while "comprising" was intended to be an open term.

III. Brakel Patent

The invention claimed in the '830 patent is placement of multiple biotin labels at the ends of a nucleotide probe as a method of improving hybridization and detection. The preferred embodiment describes the method as follows. The test sample, called the analyte, is hybridized to an "analyte-specific moiety," which is then "attached either directly or through a non-interfering linkage group with other moieties such as biotin or biotin analogues." '830 Pat. 3:5, 9, 23-25. "Detection of the analyte specific moiety" is accomplished with other chemicals, such as avidin or streptavidin, which are termed "detectable molecule[s]." Id. ll. 41-50.

A. *Claims 1, 12, 18: "Non-Radioactive Moiety"*

Claim 1 of the Brakel patent claims "[a]n oligo-or polynucleotide having at least one non-radioactive moiety directly or indirectly attached to each of the 5' and 3' end nucleotides thereof." '830 Pat. 13:63-65. Claim 12 is more specific to a "non-radioactive moiety ... attached to the 5' and 3' terminal nucleotides external to a target hybridization region...." Id. at 14:29-33. Claim 18 of the patent claims:

A method for detecting 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

Id. at 14:53-66 (emphasis added).

Both parties agree that the literal meaning of "non-radioactive moiety" is too broad, and not intended by the inventors, but they disagree on how to appropriately narrow the construction of that term. Plaintiffs' interpretation would allow the independent claims of the patent to cover direct detection methods, while defendants assert that the patent should be construed to cover only indirect detection. Specifically, plaintiffs construe the phrase "non-radioactive moiety" to mean "non-radioactive *detection* moiety," *i.e.,* interchangable with the terms "non-radioactive label" and "detection moiety" as used in the patent summary and specifications. They argue that because the dependent claims, specifically Claims 14 and 15, teach "a nucleic acid hybridization assay composition comprising an oligo-or polynucleotide of claims 1 or 12, *and* a preformed detectable molecular complex," '830 Pat. 14:37-40, which relates to indirect detection, the independent Claims 1 and 12 cannot permissibly be read to contain such a limitation.

Defendants interpret "non-radioactive moiety" to mean "a moiety capable of being detected indirectly through use of a 'preformed detectable molecular complex.' " They argue based on the method in Claim 18 that the non-radioactive moiety must be different from the directly-detectable moiety, because otherwise, step (ii) of the hybridizing method would be superfluous. They also point out that the preferred embodiment of the invention uses biotin as the non-radioactive moiety and avidin/strepavidin as the detectable molecule, illustrating that the non-radioactive moiety is a separate entity from the detectable molecule.

In this situation, the admonition against reading limitations from dependent claims into independent claims conflicts with the recognition that claim terms "are normally used consistently throughout the patent" such that "the usage of a term in one claim can often illuminate the meaning of the same term in other claims," Phillips 415 F.3d at 1314, because Claims 1 and 12 (which, when read together with their dependent claims, claim the non-radioactive moiety itself for detection) appear to use the term differently than Claim 18 (which claims use of the non-radioactive moiety plus a preformed detectable molecular complex for detection).

In such a situation, the Court relies on the fundamental principle that "claims 'must be read in view of the specification, of which they are a part.' " Id. at 1315 (citing *Markman,* 52 F.3d at 979); *see also On* Demand Machine Corp. v. Ingram Indus., Inc., 442 F.3d 1331, 1337-38 (Fed.Cir.2006) ("... the court in *Phillips,* resolving conflict, stressed the dominance of the specification in understanding the scope and defining the limits of the terms used in the claim."). The specification of the patent provides as follows. First, it defines "analyte specific moiety," the preferred embodiment of which is a nucleic acid hybridization probe. '830 Pat. 3:14-16. Then, it provides that the "analyte specific moiety" is attached "with other moieties such as biotin or biotin analogues." *Id*. at 3:25. Third,

Detection of the analyte specific moiety when attached to the analyte can be accomplished by a variety of means employing detectable molecules. Detectable molecules refer to enzymes, fluorochromes, chromogen

and the like which can be coupled to the analyte specific moiety either directly or indirectly. As an example, biotin attached to the analyte specific moiety can be detected with a preformed detectable molecule comprising avidin or streptavidin and a biotinylated enzyme. The enzyme of the resultant complex formed between the detectable molecule and the analyte specific moiety can thus serve as the signal reporting moiety of the assay composition.

'830 Pat. 3:41-53.

In context, the specification's reference to "enzymes, fluorochromes, chromagen and the like," refers to indirect detection, where such molecules are utilized to detect the "biotin or biotin analogues" attached to the probe. Furthermore, unlike the Ward patents, the four examples provided in the Brakel specification all relate to use of a biotin-avidin (or equivalent) complex, which constitutes indirect detection.

Based on the specification, therefore, the Court concludes that the "non-radioactive moiety" claimed in Claims 1, 12 and 18 must be defined as a moiety that is utilized in indirect detection, *i.e .*, a moiety that can be detected with a preformed detectable molecular complex.

IV. Stavrianopoulos Patent

The '373 patent claims a method of detecting nucleotide sequences (analytes) by fixing them on a solid support (*e.g.*, glass) and then contacting them with a labeled nucleotide probe. The signalling moiety attached to the probe is capable of generating a "soluble signal," preferably a color change or fluorescence in the solution containing the analyte.

Claim 1 of the patent claims:

A method for detecting *a polynucleotide sequence* which comprises:

fixing *said polynucleotide sequence* to a solid support ... such that a single-strand of *the polynucleotide* is capable of hybridizing to complementary nucleic acid sequences;

forming an entity comprising *said polynucleotide sequence* hybridized to a polynucleotide or oligonucleotide probe, said probe having attached thereto a *chemical label further comprising a signalling moiety* capable of generating a *soluble signal;* and

generating and detecting said soluble signal.

'373 Pat. 13:32-46 (emphases supplied).

Claim 17 claims "[a] device for detecting a polynucleotide sequence according to the method of claim 1, which device comprises a solid support, having said polynucleotide sequence fixed thereto." Id. at 14:35-38. Claim 18 claims: "[a] kit for detecting a polynucleotide sequence, which comprises the device of claim 17 in packaged combination with a container of an oligonucleotide or polynucleotide probe, having covalently attached thereto a chemical label comprising a signalling moiety capable of generating a soluble signal." Id. at 14:39-44.

A. *Claims 1, 17, 18: "Polynucleotide Sequence"*

Plaintiffs would construe "polynucleotide sequence" in these claims by the dictionary definition, as simply "a sequence of two or more nucleotides." Such a broad construction would mean that the patent would cover methods where the probe is attached to a fixed support and the labelled analyte is washed over it ("reverse dot" or "microarray" techniques, *see* Kricka Report, Ex. 10 at 19-20, 29).

Defendants "certainly [do] not dispute that the dictionary definition of a 'polynucleotide' is 'two or more nucleotides'," but argue that this simplistic definition does not address the dispute between the parties, which is whether "said polynucleotide" refers to *any* polynucleotide or only the analyte, as opposed to the probe. *See* Def. Opening Br. at 35. They would construe the term in Claims 1, 17, and 18 as "the polynucleotide sequence to be detected (*i.e.,* the analyte)." Defendants point out that the specification explains that it applies to "analytes to be detected by the detection processes of this invention ..." '373 Pat. 5:22-23. The specification further describes "[t]he hybridization of the probe to the single-stranded analyte," which has been affixed to the solid support. Id. at 5:67-68.

The plain language in Claim 1 compels the conclusion that the "polynucleotide sequence" refers to the analyte. The claim is a "method for detecting a polynucleotide sequence which comprises ... fixing *said* polynucleotide"-which obviously refers back to the polynucleotide sequence to be detected-on a solid support and then hybridizing it with a "probe." Because the second step of the method requires hybridizing a probe with "said polynucleotide," that "said polynucleotide" must be the analyte to be "detected."

The Background of the Invention section defines "analyte" as a "substance or substances ... whose presence is to be detected and, if desired, quantitated.... Among the common analytes are nucleic acids (DNA and RNA) or segments thereof, oligo-nucleotides, either single-or double-stranded, viruses, bacteria, cells in culture, and the like." '373 Pat. 1:27-36. "Probe" is defined as a "labelled polynucleotide or oligonucleotide sequence which is complementary to a polynucleotide or oligonucleotide sequence of a particular analyte and which hybridizes to said analyte sequence." Id. at 1:42-45. Thus, the definitions support the construction that the substance "whose presence is to be detected" is the analyte, *i.e.,* the unknown substance. Moreover, the probe is defined as the sequence that hybridizes with the analyte, and therefore when Claim 1 states that "said polynucleotide sequence" is hybridized with the probe, "said polynucleotide sequence" must refer to the analyte.

Accordingly, "a polynucleotide sequence" and "said polynucleotide sequence" are construed to refer to the polynucleotide sequence to be detected, meaning the analyte.

B. *Claim 1: "A Chemical Label Further Comprising a Signalling Moiety Capable of Generating a Soluble Signal"*

The more complex dispute concerning the Stavrianopoulos Patent is whether a "chemical label further comprising a signalling moiety capable of generating a soluble signal" describes light itself (plaintiffs' position) or the soluble compounds resulting from the action of the enzyme label on a soluble substrate that can be measured by use of light, *i.e.,* a spectrophotometer (defendants' position).

Plaintiffs would construe "soluble signal" in Claim 1 as "a signal which does not precipitate and is thus detectable by spectrophotometric and/or colormetric assay techniques, such as for instance, colormetric, photometric and fluorescent signals." They derive support for their construction from several dependent claims. Claims 2 and 13 claim a "detecting step [that] comprises spectrophotometric techniques." '373 Pat. 13: 48-49. Claims 3 and 15 claim that the "soluble signal is selected from the group consisting of a colored

product, a chemiluminescent product and a fluorescent product," while claim 19, which depends from an experiment "kit" claimed in 18, states that the "soluble signal is a colored product or a fluorescent product." Additionally, the specification teaches that "[t]he method of the present invention involving the colorimetric or photometric determination of the hybridized probes employs as the signalling moiety reagents which are capable of generating a soluble signal, *e.g.,* a color change in a substrate in solution." Id. at 6:9-13. Plaintiffs argue that because these dependent claims suggest that the soluble signal is a color or a fluorescence or can be detected with spectrophotometer, the soluble signal can include light.

Defendants construe "soluble signal" as a "soluble *compound* dissolved in solution," and would require that "the label includes a portion capable of producing a detectable *compound*." They emphasize the scientific definition of "soluble" as "capable of being dissolved," and argue that Enzo's construction is scientifically illogical because light cannot be dissolved. They would define the signal as the color change of a "compound in solution," not a property of the signalling moiety itself. Defendants' expert explains that Table 1 in the specification of the '373 patent, which lists "exemplary components" for the label and substrate, lists combinations that react to form water-soluble colored or fluorescent molecules. *See* Kricka Report at 37. Finally, defendants criticize plaintiffs for impermissibly reading the term "soluble" out of the phrase "soluble signal," and argue that the inventors would not have distinguished between soluble and insoluble signals (*i.e.,* precipitates) if any signalling moiety were covered by the claims.

It is evident from the parties' arguments and expert reports that the term "soluble signal" would have no established meaning to one skilled in the art. *See* Krika Report at 35 ("In my opinion, a skilled person in 1983 would not have readily understood the term 'soluble signal.' Solubility is not a characteristic that is normally associated with a signal in general.") In this instance the inventors were their own lexicographers. The term they invented, however, is ambiguous given applicable scientific principles which, as defendants point out, instruct that the signal the inventors had in mind-light (including color)-is not "soluble" because it does not dissolve in solution. On the other hand, defendants' definition of "soluble signal" as "a detectable *compound* dissolved in solution" finds no basis in the claims or specification, which do not use the term "compound" and in fact suggest that the inventors intended "signal" to refer to light, which is not a compound. The Court's task therefore is to construe the term "soluble signal" giving effect to both of the words in that phrase.

The background of the invention defines "Signal" as "The *characteristic* of a label or signalling moiety that permits it to be detected from sequences that do not carry the label or signalling moiety." '373 Pat. 1:66-68. The technique for determining the presence and quantity of the signalling moiety is consistently referred to in the specification as "colorimetric or photometric determination," *see, e.g.,* id. at 6:10; 7:15; 8:56, and one example of "a soluble signal" consistently given in the specification is "a color change in a substrate in solution." Id. at 6:13. The advantage of the inventors' techniques, they claimed, was that previous techniques using "insoluble 'signals', *i.e.,* precipitates, certain fluorescers, and the like ..., only provide detection not quantitation." Id. at 4:43-44. Thus it appears that they did not intend to limit the "signal" to simply a " *detectable* compound," but were concerned with the *characteristics* of the signal that would allow it to be used to quantify the amount of probe that had hybridized with the analyte. While defendants may be correct that the exemplary components for the signalling moiety listed in Table 1 (col.6) of the patent all involve compounds that would dissolve in solution, these were given only as examples, and the inventors clearly believed that the primary aspect of their invention was "the *colorimetric or photometric* determination of the hybridized probes ... which are capable of generating a soluble signal, *e.g.,* a color change in a substrate in solution." '373 Pat. 6:9-13 (emphasis supplied). Thus, the Court concludes: (1) the inventors wanted to distinguish their invention from previous methods utilizing insoluble signals such as precipitates; but (2)

they were less concerned with the solubility of the signal than the method of detection, including colorimetric and photometric techniques.

Therefore, although neither party's proposed construction of the term "soluble signal" is entirely satisfying-because the term itself has no inherent meaning outside of this patent-the Court adopts plaintiffs' definition of "soluble signal" as "a signal that does not precipitate and is thus detectable by spectrophotometric and/or colormetric assay techniques, such as colormetric, photometric and fluorescent signals."

C. *Claim 1: "A Chemical Label Further Comprising a Signalling Moiety"*

Finally, the parties dispute whether the "chemical label" of Claim 1 must consist exclusively of the "signalling moiety capable of generating a soluble signal," or whether, as plaintiffs argue, the label need only include a portion that provides a signal for detection and may include other parts as well.

The patent defines the term "label" as follows:

Label-That moiety attached to a polynucleotide or oligonucleotide sequence which comprises a signalling moiety capable of generating a signal for detection of the hybridized probe and analyte. *The label may consist only of a signalling moiety,* e.g ., an enzyme attached directly to the sequence. *Alternatively, the label may be a combination of a covalently attached bridging moiety and a signalling moiety or a combination of a non-covalently bound bridging moiety and signalling moiety* which gives rise to a signal which is detectable, and in some cases quantifiable.

'373 Pat. 1:45-56 (emphases supplied).

The patent defines a "signalling moiety" as "[t]hat *portion* of a label which on covalent attachment or non-covalent binding to a polynucleotide or oligonucleotide sequence or to a bridging moiety attached or bound to that sequence provides a signal for detection of the label." '373 Pat. 1:61-65 (emphasis supplied).

Together, the two definitions clearly show that a signalling moiety may be a part but not the whole of a label. More specifically, a label may consist of a single signalling moiety or a combination of a signalling moiety and a bridging moiety. Where the specification provides a definition of a claim term, that definition controls. *See* Phillips, 415 F.3d at 1316 ("[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs.").

This reading is supported by the fact that the term "bridging moiety" is nowhere to be found in any of the claims, yet the specification defines "bridging moiety," '373 Pat. 1:57-60, and teaches methods for utilizing such a bridging moiety to join the signalling moiety to the nucleotide sequence portion of the probe, as well as the preferred bridging moieties to be used, *see id*. at 2:11-64. If a "label" consisted entirely of a "signalling moiety," these portions of the specification involving bridging moieties would be read out of the patent entirely.

Accordingly, the Court adopts plaintiffs' definition of "a chemical label further comprising a signalling moiety" as "a chemical label including, but not limited to, a portion that provides a signal for detection." FN6

FN6. Consistent with its definition of "soluble signal," *supra* s. IV.B, the Court also declines defendants' invitation to read the term "detectable *compound* " into the definition of this term.

V. Conclusion and Certification for Appeal

The disputed claim terms are hereby construed as described above. Pursuant to 28 U.S.C. s. 1292(b), the Court certifies the foregoing ruling for immediate appeal to the Federal Circuit, recognizing that its construction of the disputed claims in the Ward patents (Claim 1, patents '767, '824, '928, and ' 955) and the Stravrianopoulos patent (Claim 1, patent '373) conflicts with the construction of the same patents issued recently by the Southern District of New York, Enzo Biochem, Inc. v. Amersham PLC, 439 F.Supp.2d 309 (S.D.N.Y.2006) (Sprizzo, J.), and finding "that an immediate appeal ... may materially advance the ultimate termination of the litigation" in both cases. 28 U.S.C. s. 1292(b).

IT IS SO ORDERED.

D.Conn.,2006.
Enzo Biochem, Inc. v. Applera Corp.

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