United States District Court,
N.D. California.

AFFYMETRIX, INC., a Delaware corporation,
Plaintiff and Counterdefendant.
v.
MULTILYTE LTD., a British corporation,
Defendant and Counterclaimant.

No. C 03-03779 WHA

April 28, 2005.

George C. Yu, Michael J. Malecek, Esq., Daniel Raymond Reed, Affymetrix, Inc., Emeryville, CA, Darin Jeffrey Glasser, John Christopher Kappos, O'Melveny & Myers LLP, Newport Beach, CA, Diane K. Wong, Polaphat Veravanich, O'Melveny & Myers, LLP, Irvine, CA, George A. Riley, O'Melveny & Myers, San Francisco, CA, for Plaintiff and Counterdefendant.

Christine Saunders Haskett, Heller Ehrman, LLP, San Francisco, CA, Kalai Lau, Leonard J. Feldman, Mark S. Parris, Heller Ehrman LLP, Seattle, WA, Michael K. Plimack, Samuel F. Ernst, Heller, Ehrman, LLP, for Defendants and Counterclaimant.

ORDER GRANTING MULTILYTE'S MOTION FOR FURTHER CLAIM CONSTRUCTION AND RE-CONSTRUING "BINDING AGENT"

WILLIAM ALSUP**, District Judge.**

INTRODUCTION

Multilyte moves for further claim construction on the term "binding agent," as it is used in United States Patent Nos. 5,599,720 ("the '720 patent"), 5,432,099 ("the '099 patent") and 5,807,755, ("the '755 patent"), for which reexamination proceedings are still pending. This order **GRANTS** the motion and re-construes the term "binding agent."

STATEMENT

Following a technology tutorial, two rounds of briefing and a *Markman* hearing, the Court issued its Order Construing Selected Claim Terms on February 22, 2005. Therein, four disputed phrases were construed: (1) "binding agent;" (2) "determining the ambient concentrations;" (3) "loading a plurality of different binding agents ... onto a support means;" and (4) "a plurality of spaced apart small spots."

The term "binding agent," used synonymously in each of the three patents-in-suit, was construed to mean "a molecule used in an immunoassay that is capable of binding to an analyte and has an affinity constant (measured at equilibrium) of 10^{13} liters/mole or less" (Cl. Const. Order at 6-11). Because there was insufficient information in the record at that time, that order declined to rule whether oligonucleotides were included or excluded from the definition of "binding agent."

In the joint status-conference statement filed on March 1, 2005, the parties agreed that further claim

construction on the term "binding agent" would be case-dispositive. Following the status conference on March 3, 2005, a second case-management order was issued, granting Multilyte leave to file a motion for further claim construction of "binding agent." In addition, Affymetrix was granted leave to file two summary-judgment motions, which are addressed by separate order.

ANALYSIS

By granting Multilyte leave to file a motion for further claim construction, the Court was anticipating evidence on whether oligonucleotides could be used as binding agents in immunoassays or had affinity constants of 10^{13} liters/mole or less. In other words, the parties were expected to argue whether "binding agent," as already defined, would include or exclude molecules comprised of nucleic acids. The Court is disappointed that Multilyte took the liberty of interpreting the second case management order as an invitation to file a motion for *reconsideration* of the claim-construction order. If Multilyte had intended to file such a motion, it should have complied with Civil Local Rule 7-9(b). It did not.

That said, this order recognizes that the definition of "binding agent" previously adopted was inadvertently too narrow. "Binding agent" was not intended to be limited to the preferred embodiments, namely antibodies. But, to the extent that the previous claim-construction order was internally inconsistent, Multilyte has only itself to blame. At the claim-construction hearing, Multilyte's counsel *unequivocally* confirmed that the other types of binding agents referenced in the '720 patent, (*i.e.*, binding proteins and receptor preparations), were also used in immunoassays (Kappos Exh. 2 at 32:18-25). FN1 The Court relied on this response in framing its construction. Because counsel answered "yes" without any hesitation, the Court naturally concluded that defining a "binding agent" as "a molecule used in an immunoassay" would encompass the use of a binding protein or a receptor preparation to determine the ambient concentration of a hormone.

FN1. Unless otherwise indicated, citations refer to the declarations and exhibits proffered with respect to Multilyte's Motion for Partial Summary Judgment for Further Claim Construction of the Term "Binding Agent."

After the order was issued, Multilyte reversed field and now argues that its answer at oral argument was scientifically inaccurate (Br. 7, stating "Multilyte regrets to inform the Court that counsel should have answered this question in the negative and regrets any confusion this may have caused."). It presents evidence that immunoassays require either the binding agent or the analyte to be an antibody or an antibody fragment (*See* Kricka Decl. and appended exhibits). Affymetrix argues that "binding agent" was properly construed. It agrees with Multilyte that all immunoassays use antibodies and has moved for summary judgment on the basis that the accused products do not.

That immunoassays *always* involve the use of antibodies as either the binding agent or the analyte is a highly material fact. While it is unclear why the parties could not have presented this evidence earlier, the Court wishes to avoid an inconsistent construction of the term "binding agent." Affymetrix has proffered a creative explanation that would resolve the apparent contradiction (Opp.3-12). It argues that no reconsideration of the term "binding agent" is necessary because the antibody (or antibody fragment) in an immunoassay can be either the binding agent or the analyte. Thus, other types of molecules can be used as binding agents whenever the analyte is the antibody specific for that molecule. This argument is rejected. As described above, it was the Court's intention to include the type of assay wherein a binding protein or a receptor fragment is used to determine the ambient concentration of a hormone. Accordingly, despite the way in which Multilyte has behaved, its motion for reconsideration is **GRANTED.**

1. "binding agent"

"Binding agent" is now construed to mean "a molecule conventionally having one or at most two binding sites and an affinity constant (measured at equilibrium) of 10^{13} liters/mole or less." This order incorporates by reference the reasoning employed in the claim-construction order of February 22, 2005. As previously noted, there is no doubt that the primary focus of the patents-in-suit was improving immunoassays. Throughout the patent specifications and prosecution histories, the inventor emphasized immunoassays; indeed, the term "binding agent" was often used interchangeably with "antibody." Thus, the most natural claim construction would limit "binding agent" to molecules used in immunoassays, as the prior order concluded.

From that starting point, Multilyte cannot now expand the scope of the invention to encompass *all* types of biological binding assays or ligand binding assays. To the extent that other types of assays were mentioned, even in passing, this order finds that the patents-in-suit provide support for only *some* assays in addition to immunoassays. FN2

FN2. While the previous claim-construction order already expressed concern regarding whether such embodiments were sufficiently enabled because they were merely mentioned as hypothetical alternatives to antibodies, the question of patent validity is not currently before the Court, so Multilyte is given the benefit of the doubt for the purposes of this order.

The only other binding agents explicitly referenced in the three patents were binding proteins or receptor preparations ('720 patent at col. 3:61-65). These molecules are structurally and functionally similar to antibodies in that they are also proteins with highly specific binding sites. FN3 Rather than limit "binding agent" to those molecules used in immunoassays, this order relies upon the language most closely resembling a definition provided by the patentee himself. The ' 099 patent and the ' 755 patent parenthetically define the term "binding agent" as follows: "each molecule of binding agent conventionally having one or at most two binding sites" (' 099 patent at col. 1:62-63; ' 755 patent at col. 1:63-65). As previously noted, the specifications then elaborated that "[f]or specific binding agents of the very highest affinity K is less than 10^{13} liters/mole" (' 099 patent at col. 2:14-15; ' 755 patent at col. 2:15-16). The revised construction of "binding agent" takes into account both of these limitations.

FN3. Multilyte's expert conceded that antibodies are also proteins that exhibit specific binding activity, although the term "binding protein" is typically used to refer to a specific binding protein, such as thyroxine binding globulin (Kappos Exh. 6 at 140:6-25).

To avoid any possible confusion, this order clarifies that this definition of "binding agent" includes (but is not limited to) antibodies, binding proteins and receptor preparations. On the other hand, this definition does *not* encompass DNA, RNA, oligonucleotides or any other molecules comprised solely of nucleic acids. It is true that the patentee explicitly contemplated "[a] wide variety of binding agents may also be used provided that they have binding sites which are specific for the analyte in question" ('720 patent at col. 3:54-56). FN4 But, as explained below, only proteins have "binding sites" in the biological sense of the word.

FN4. In the previous claim-construction order, this excerpt was mistakenly cited to the '099 patent instead of the '720 patent.

2. "binding site"

A "binding site" is generally understood to be the region of a *protein* that is capable of binding to an analyte (*See* Plimack Declaration in Opposition to Affymetrix' Motions for Summary Judgment Exh. A at 6) ("The region of the protein that associates with other molecules is called the binding site"). The fundamental

source of disagreement with regard to the construction of "binding agent" seems to revolve around whether the term "binding site" should be given its biological meaning (*i.e.*, a structurally and functionally distinct region of a protein) or the broader non-scientific, plain-language meaning (*i.e.*, any site where binding occurs). This order chooses the former.

First, nowhere in the specifications or prosecution histories did the patentee indicate an intent to deviate from the scientific meaning of "binding site" typically used by immunologists and other biologists. Absent an express definition in the specification, the term "binding site" must be given the ordinary meaning as understood by a person of ordinary skill in the relevant art. Zelinski v. Brunswick Corp., 185 F.3d 1311, 1315 (Fed.Cir.1999). As described above, the preferred embodiment of a "binding agent" was an antibody; only two other embodiments were explicitly mentioned and both were proteins. Neither oligonucleotides nor any other non-protein molecules were mentioned as a potential embodiment of the invention anywhere in the intrinsic evidence.

Second, the evidence proffered by Multilyte to demonstrate that DNA or RNA can have "binding sites" is inapposite. Its references all describe nucleotide interactions with *proteins* (or protein complexes), rather than a complementary sequence of base pairs (*See* Purdue Reply Declaration in Support of Multilyte's Claim Construction Reply Brief and appended exhibits). FN5 While this order recognizes that the region within a nucleic acid sequence recognized by a protein's "binding site" is itself referred to as a "binding site," Multilyte has presented no evidence that regions where *two oligonucleotides hybridize with each other* are ever called "binding sites" by persons of skill in the relevant art.

FN5. The examples described therein included: ribosomes, reverse transcriptase, U1 snRNP, Sp1, C/EBP, AP1, OCT-1, OCT-2, E12, E47, E2-2, repressor proteins and IRP. Of these, only the binding of U1 snRNA and its target sequence in pre-mRNA could possibly be confused as an interaction between two oligonucleotides, but a closer reading of the article reveals that U1 snRNA is merely a subunit of the larger ribonucleoprotein U1 snRNP (*See* Purdue Reply Decl. Exh. D).

Third, all of the scientists whose depositions were proffered experienced difficulty applying the term "binding site" to an oligonucleotide, unless they assumed the non-scientific, plain-meaning definition. Dr. Edwin Ullman, an expert for Affymetrix, emphasized that "[t]he term 'binding sites' is usually not used with respect to nucleic acids, except with reference to their binding to proteins" (Plimack Declaration in Opposition to Affymetrix' Motions for Summary Judgment Exh. C at 352:3-10). When pressed, he reasoned that two complementary nucleic acid strands could each have "a binding site which recognizes the other," but added the caveat that "[w]e're now somewhat distorting the term 'binding site,' so I need to caution us that binding sites in proteins are defined, rigid structures, and we've now used the term in a somewhat different way, certainly a different way than the patents we're considering" (*id.* at 353:3-21). FN6 He later clarified that the patents never defined "what a binding site of a nucleic acid is," but "[n]ucleic acids are generally not considered to have binding sites per se" (Yu Declaration in Support of Affymetrix, Inc.'s Reply to Motion for Summary Judgment Exh.4 at 334:19-25).

FN6. Although Multilyte failed to mention this during the hearing, the deposition testimony of Dr. Ullman it referenced during oral argument was on the same page as this caveat.

Multilyte's witnesses had the same problem. One of its experts, Dr. Paul Purdue, also testified that the term "binding site" had a different, more flexible meaning when applied to nucleotide sequences, depending on the sequence of the opposite strand (*id.* Exh. E at 77:2-25). FN7 Even the inventor himself, Dr. Roger Ekins, found it difficult to quantify how many binding sites a particular strand of nucleic acids might have; he called it a "philosophical question" and suggested that the binding site in DNA could be the entire strand, an individual nucleotide or any combination of contiguous nucleotides in the sequence (Kappos Declaration

in Support of Affymetrix, Inc.'s Motions for Summary Judgment Exh.1 at 214:16-215:15).

FN7. Multilyte's other expert, Dr. Larry Kricka, did not focus on the term "binding site."

Finally, even if there existed genuine ambiguity as to what "binding site" meant, the Court would have to resolve it against the drafter of the patent and adopt the more restrictive meaning. Athletic Alternatives v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed.Cir.1996). Thus, this order finds that a "binding site" is the region of a protein capable of binding to an analyte, such that it effectively limits the claim term "binding agent" to cover only this subclass of molecules or fragments thereof.

CONCLUSION

For the reasons stated above, Multilyte's motion for reconsideration of the term "binding agent" is **GRANTED.** "Binding agent" is re-construed to mean "a molecule conventionally having one or at most two binding sites and an affinity constant (measured at equilibrium) of 10^{13} liters/mole or less." This definition expressly *includes* antibodies, binding proteins, receptor fragments and other proteins or protein fragments, but *excludes* DNA, RNA, oligonucleotides and any other molecules comprised solely of nucleic acids. This ruling shall govern all subsequent proceedings as to this term.

IT IS SO ORDERED.

N.D.Cal.,2005.
Affymetrix, Inc. v. Multilyte Ltd.