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

Feb. 22, 2005.

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

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

ORDER CONSTRUING SELECTED CLAIM TERMS

WILLIAM ALSUP**, District Judge.**

INTRODUCTION

After a technology tutorial, followed by two rounds of briefing leading up to the *Markman* hearing, this is a claim-construction order for selected claim terms in United States Patent Nos. 5,599,720, 5,432,099 and 5,807,755. Although reexamination proceedings are still pending, the parties have identified four phrases which are likely to appear in any claims that are ultimately allowed.

STATEMENT

Plaintiff Affymetrix, Inc. is a Delaware corporation with its principal place of business in Santa Clara, California. Plaintiff manufactures and sells DNA microarray systems under the trade name GeneChip(R). Defendant Multilyte Ltd. is a British Corporation with its principal place of business at the Division of Molecular Endocrinology, University College London Medical School. Multilyte is the assignee of a series of patents listing Roger P. Ekins, a professor in that school, as the inventor.

There are three patents at issue. The first is United States Patent No. 5,599,720, ("the '720 patent"), entitled "Measurement of Analyte Concentration." The second is United States Patent No. 5,432,099, ("the '099 patent"), entitled "Determination of Ambient Concentration of Several Analytes." The last is United States Patent No. 5,807,755, ("the '755 patent"), bearing the similar title "Determination of Ambient Concentrations

of Several Analytes." FN1

FN1. These patents are provided as Haskett Decl. Exhs. A, B, and C respectively. This order only cites the '099 patent, but the specification of the '755 patent is nearly identical.

The '720 patent, filed on June 17, 1994, is the surviving offspring of three continuation applications, each of which was abandoned. The original application in this sequence was filed on April 24, 1984. The '755 patent, filed on May 23, 1995, is a continuation-in-part of the '099 patent, filed on December 1, 1992, which was itself a continuation of another patent application, filed on August 5, 1988, and subsequently abandoned. As such, the specifications of the '099 patent and the '755 patent are nearly identical.FN2

FN2. Because these two specifications are nearly identical, this order only cites the '099 patent.

Affymetrix filed this declaratory judgment action on August 13, 2003, but subsequently amended the complaint several times; most recently, the fourth amended complaint was filed on April 7, 2004, alleging non-infringement, invalidity and unenforceability of defendant's patents. In response, Multilyte answered on April 21, 2004, and asserted counterclaims of infringement, which were answered by Affymetrix on May 11, 2004.

Back on December 12, 2003, the Court granted a partial stay as to any motions on the merits (*i.e.*, summary judgment or preliminary injunction motions), while the reexamination proceedings were pending. This partial stay did not apply to discovery or other pretrial matters, including claim construction. Later, on May 27, 2004, *all* proceedings were stayed, contingent upon Multilyte agreeing not to commence any court or ITC proceeding in the United States on the three patents-in-suit. Multilyte agreed to this condition and the deadlines set forth in the case management order were vacated on June 3, 2004. On December 2, 2004, the parties appeared for a status conference. At that time, they indicated that not only were there *multiple* reexamination proceedings already in progress, but even more had been requested by Affymetrix. In light of this revelation and to avoid prolonging the stay indefinitely until *all* the reexaminations have been completed, the Court has decided to cautiously proceed with claim construction, at least as to claims that have emerged from the reexamination process thus far.

ANALYSIS

This order construes four disputed phrases which are likely to appear in any claims ultimately allowed: (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."

In interpreting the disputed terms, it is useful to appreciate the background art as described in the specification. The technology described therein relates to assays used by life-sciences researchers to detect the concentration of analytes, (*i.e.*, hormones, proteins or other substances), in biological liquids such as saliva, serum, blood and urine. The parties have stipulated that "analyte" means "the substance to be measured and/or detected."

By the mid-1980s, when Dr. Ekins first sought patent protection, methods for measuring the concentration of analytes using binding agents with specific binding sites were well known. Before the invention,

however, it was generally believed that for more accurate results, relatively large amounts of binding agent should be used, such that approximately 50% or more of the analyte in the sample would be bound ('099 patent at cols. 1:48-2:42). Thus, it was often necessary to know the precise volume of the sample order to accurately determine the concentration of the analyte therein (ibid.). To control the volume of the samples, such assays had to be performed in vitro ('720 patent at col. 2:1-10).

Dr. Ekins realized that "the occupancy of the binding sites by the analyte (*i.e.,* the proportion of binding sites occupied by the analyte on the binding agent) [wa]s independent of the absolute volume of the fluid and the absolute number of binding sites, and hence independent of the absolute amount of binding agent" (id. at col. 2:24-28). This was, he asserted, a surprising observation. "Indeed, many experienced immunologists, when first introduced to the methodology of the present invention cannot immediately understand why it is that amounts of analyte vastly in excess of the amount of antibody in the system do not result in total occupancy of all antibody binding sites and that the fractional occupancy of these sites serves as a measure of analyte concentration" (Haskett Decl. Exh. L at 9; *see also* Kappos Decl. Exh. 6 at 2).

Even though the reason *why* was not completely understood, the use of very small amounts of binding agent had the unexpected advantage of obtaining "reliable and sometimes even improved estimates of analyte concentration" without having to measure the exact volume of each sample, such that assays could now be performed *in vivo* ('099 patent at col. 3:6-18). This insight also made possible the development of "multi-analyte" and "microarray" assays that use small amounts of multiple binding agents on a single solid support to detect different analytes simultaneously (id. at cols. 3:47-4:18).

The '099 patent and the '755 patent focused on such methods of determining the concentrations of a plurality of analytes. In contrast, the ' 720 patent was directed at the underlying method of determining the concentration of a single analyte using a small amount of binding agent. As mentioned above, reexamination of these patents is still ongoing. The first office actions were all dated July 8, 2004. Thus far, no claims of the '720 patent have been allowed (Kappos Decl. Exh. 23). Claims 1-11 of the '099 patent, however, were allowed (Kappos Decl. Exh. 26). Likewise, Claims 1-8 of the '755 patent were also allowed (Haskett Supp. Decl. Exh. B).

Of these, the independent claims are Claim 1 of the '099 patent and Claims 1 and 4 of the '755 patent. These claims are reproduced below, with the disputed phrases italicized.

The '099 patent

1. A method for *determining the ambient concentrations* of a plurality of analytes in a liquid sample of volume V liters, comprising:

loading a plurality of different binding agents, each being capable of reversibly binding an analyte which is or may be present in the liquid sample and is specific for said analyte as compared to the other components of the liquid sample, *onto a support means at a plurality of spaced apart small spots* such that each spot has a high coating density of one of said *binding agents* but not more than 0.1 V/K moles of *binding agent* are present on any spot, where K liters/mole is the affinity constant of said *binding agent* for said analyte;

contacting the loaded support means with the liquid sample to be analyzed, such that each of the spots is contacted in the same step with said liquid sample, the amount of liquid used in said sample being such that only an insignificant proportion of any analyte present in said liquid sample becomes bound to said *binding*

agent specific for said analyte, and

measuring a parameter representative of the fractional occupancy by said analytes of said binding agents at the spots by a competitive or non-competitive assay technique using a site-recognition reagent for each *binding agent* capable of recognizing either the unfilled binding sites or the filled binding sites on said *binding agent,* said site-recognition reagent being labelled with a marker enabling the amount of said reagent in the particular location to be measured ('099 patent at col. 13:22-54).

The '755 patent

1. A method for *determining the ambient concentration* of an analyte of interest among a plurality of analytes in a liquid sample of volume V liters, comprising:

loading a plurality of different binding agents, each being labelled with a marker and being capable of reversibly binding an analyte which is or may be present in the liquid sample and is specific for said analyte as compared to the other components of the liquid sample, *onto a support means at a plurality of spaced apart small spots* such that not more than 0.1 V/K moles of *binding agent* are present on any spot, where K liters/ mole is the affinity constant of said *binding agent* for said analyte;

contacting the loaded support means with the liquid sample to be analyzed, such that each of the spots is contacted in the same step with said liquid sample, the amount of liquid used in said sample being such that only an insignificant proportion of any analyte present in said liquid sample becomes bound to said binding agent specific for said analyte;

contacting the support with a site-recognition reagent specific for each *binding agent* in a competitive or non-competitive technique, the site-recognition reagent being capable of recognizing either the unfilled binding sites or the filled binding sites on said *binding agent,* said site-recognition reagent being labelled with a marker different from the marker on said *binding agent,* and

measuring a ratio of signals from said markers on the site recognition reagent and the binding reagent from at least a part of the spot, from which the analyte to interest is determined ('755 patent at cols. 14:40-15:4).

4. A method for determining the fractional binding site occupancy of a plurality of *binding agents* by a plurality of analytes in a liquid sample of V liters, comprising:

(a) *loading a plurality of different binding agents,* each being capable of reversibly binding an analyte which is or may be present in the liquid sample and is specific for said analyte as compared to the other components of the liquid sample, *onto a support at a plurality of spaced apart small spots* such that each spot has a high coating density of one of said *binding agents* but not more than 0.1 V/K moles of binding agent are present on any one spot, where K liters/mole is the affinity constant of said *binding agent* for said analyte;

(b) contacting the loaded support with the liquid sample to be analyzed, such that each of the spots is contacted in the same step with said liquid sample, the amount of liquid used in said sample being such that only an insignificant proportion of any analyte present in said liquid sample becomes bound to said *binding agent* specific for said analyte; and

(c) thereafter contacting the loaded support with site-recognition reagents which recognize either the unfilled binding sites or filled binding sites of that binding agent, the site-recognition reagents being labelled with markers from which the fractional binding site occupancy for each *binding agent* is determined (id. at col. 15:11-36).

1. "binding agent"

Any claim ultimately allowed (after *all* the pending reexamination proceedings are completed) will surely contain the term "binding agent." The parties agree that "binding agent" means the same thing in each of the three patents-in-suit. Multilyte argues that this phrase should be construed broadly as "a molecule having a site or sites that bind to another substance." Affymetrix proposes the construction "a protein, especially an antibody, that is capable of specific binding." Both proffered constructions are rejected.

This order holds that "binding agent" means "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." An immunoassay is a type of assay used by life-sciences researchers for identifying and quantifying organic and inorganic compounds. An immunoassay typically uses antibodies to bind antigens, but other molecules may also be used as the binding agent. This order declines to explicitly hold whether DNA or other molecules comprised of nucleic acids are included or excluded from the definition of "binding agent." There is currently insufficient evidence for the Court to evaluate whether such molecules may be used in immunoassays or whether their binding affinities are less than 10^{13} liters/mole.

The Federal Circuit has repeatedly warned that there is sometimes a fine line between reading a claim in light of the specification and reading a limitation into the claim from the specification. Comark Comms. v. Harris Corp., 156 F.3d 1182, 1187 (Fed.Cir.1998) (citations omitted). While this order acknowledges that it would be impermissible to read the disclosed embodiments into the claims without other indicia that the patentee so intended to limit the invention, that is not the case here. Because the specification as a whole makes it clear "that the claimed invention is narrower than the claim language might imply, it is entirely permissible and proper to limit the claims" accordingly. Alloc, Inc. v. Int'l Trade Comm'n, 342 F.3d 1361, 1370 (Fed.Cir.2003).

Even a cursory reading of the patents-in-suit reveals that the invention was directed at improving the immunoassays which were in use when the patent applications were filed (and still are). For example, the very first sentence summarizing the invention stated that "[t]he present invention involves the realisation that the use of high quantities of binding agent is neither necessary for good sensitivity in immunoassays nor is it generally desirable" ('099 patent at col. 3:3-6). Indeed, "[t]he concept of using only a trace amount of binding agent [as described in the patent] is contrary to generally recommended practice in the field of immunoassay and immunometric techniques" (id. at col. 1:48-51). The '720 patent even named the potential "high sensitivity, multiple-analyte assay" described therein an "immunometer" ('720 patent at 6:60-7:10).

The prosecution history also emphasized that "the methodology embodied in the present invention contravene[d] currently accepted views of immunoassay design" (Haskett Decl. Exh. L at 9). In addition, during a "group discussion with Examiners Grun, Chin and Woodward" to explain the underlying principles of his methodology, Dr. Ekins consistently referred to his invention as an "ambient-analyte immunoassay" (Kappos Decl. Exh. 7 at 6 and attached slides at 35 *et. seq.*).

It is undisputed that antibodies were the preferred embodiment. "The binding agents used will preferably be

antibodies, more preferably monoclonal antibodies" ('099 patent at col. 6:44-45). The patents consistently characterized the binding agent as having "one or at most two binding sites" or "two binding sites per molecule," which is a structure expected of antibodies (id. at cols. 1:61-63; 2:12-14). The '720 patent also consistently referred to the affinity constant of the chosen binding agent as "K_{ab}," where "ab" is shorthand for antibody ('720 patent at col. 5:18-23). It was further noted that "[a]ffinity constants for many commercially available binding agents are already a matter of record," but "[i]f the constant is not already known for a particular *antibody,* it maybe determined by a standard Scatchard analysis ..." (id. at col. 5:66-6:2) (emphasis added).FN3

FN3. The affinity constant, K, is a measure of the ratio of bound to unbound molecules at equilibrium.

Affymetrix's proposed construction limits the "binding agent" to proteins, especially antibodies. Without evidence that only *proteins* are used in immunoassays, which has not yet been presented to the Court, this order declines to adopt such a definition. The method described in the patents "may be used for the estimation of analytes of all types provided that a specific binding agent is available" and conversely, "[a] wide variety of binding agents may also be used provided that they have binding sites which are specific for the analyte in question" ('099 patent at col. 3:20-21, 54-56). The definition of "binding agent" is not limited to the preferred embodiments.

On the other hand, Multilyte's proffered definition, which would include molecules used in *any* type of assay, is too broad. Though this order finds that the invention is not limited to antibodies, even the other types of "binding agents" described, (*i.e.,* binding proteins or receptor preparations), were intended for use in immunoassays ('720 patent at col. 3:61-65).FN4 This, as well as the specification as a whole, evinced a clear intent to limit the scope of "binding agent" to molecules used in immunoassays. The patents also explicitly limited the "binding agent" to molecules having an affinity constant of 10^{13} liters/mole or less ('099 patent at col. 2:14-15) ("For specific binding agents of the very *highest* affinity K is less than 10^{13} liters/mole") (emphasis added).

FN4. At oral argument, counsel for Multilyte confirmed that antibodies, binding proteins and receptor preparations were all used in immunoassays.

Nowhere in the specifications or prosecution histories of the patents is there any indication that the phrase "binding agent" was intended to encompass molecules beyond those used in immunoassays. First, the intrinsic evidence does not even allude to other types of assays. Second, even if other types of assays had been mentioned, it is unclear whether such embodiments would be enabled. "[I]t is well recognized that for complex biological processes a reference to known general techniques does not establish whether or how such techniques may be successfully adapted to a particular activity." Biogen, Inc. v. Berlex Labs., Inc., 318 F.3d 1132, 1137 (Fed.Cir.2003) (limiting the invention to the single DNA construct described in the specification and excluding viral vectors that had been mentioned).

Moreover, as Affymetrix pointed out during oral argument, pre-existing pH assays had already used small amounts of binding agent to determine the ambient concentration of hydrogen ions [H] in solution. Thus, expanding the scope of "binding agent" beyond molecules used in immunoassays also risks invalidating the '720 patent as anticipated. Because "claims should be so construed, if possible, as to sustain their validity," this order declines to do so. Rhine v. Casio, Inc., 183 F.3d 1342, 1345 (Fed.Cir.1999) (citations omitted).

Multilyte specifically requests a claim construction that specifically includes " *inter alia,* nucleic acids and oligonucleotides." (This is driven by the fact that the products made by Affymetrix are DNA-based.) In support, Multilyte has proffered both expert testimony and extrinsic evidence that DNA was also considered a binding agent by those skilled in the art at the time of the invention (*see e.g.,* Br. 7-10; Kricka Decl. Exh. B at 7, 76-77; Kricka Reply Decl. Exh. D at col. 4:3-30). In response, Affymetrix argues that even if "binding agent" is not limited to proteins, the binding affinity of DNA is greater than 10^{13} liters/mole, a fact which was recognized by the inventor himself.FN5 Multilyte has countered with evidence that at least *some* DNA is not outside this range, although it appears to the Court that all of the proffered references referred to an apparent or measured binding affinity, rather than the affinity constant at equilibrium (*see* Kricka Reply Decl. Exhs. I-L).FN6

FN5. In a letter addressed to Dr. Hans Berger at Boehringer Mannheim, Dr. Ekins noted that "affinity constants of DNA probes (as measured at equilibrium) are in the region of 10^{17}-10^{20} L/M," although "if measured after shorter incubation times, the *apparent or measured* affinities are obviously less" (Kappos Decl. Exh. 12) (emphasis in original).

FN6. At equilibrium, there is no net change in the ratio of bound to unbound molecules. When the binding affinity is measured after a shorter incubation time, before the system reaches equilibrium, it will appear lower because fewer molecules will be bound.

The Court declines to rule whether nucleic acids and oligonucleotides are "binding agents." First, it is unclear whether any of the evidence proffered by Multilyte demonstrates that DNA could be used as the binding agent in an immunoassay. To the extent that DNA is only used in other types of assays, it would be excluded from the definition of "binding agent." Second, even assuming *arguendo* that the binding affinity of DNA is sometimes less than 10^{13} liters/mole, this would mean that *some* DNA probes could be "binding agents" but others would not. Thus, it would be inappropriate to categorically include or exclude nucleic acids and oligonucleotides in the definition of "binding agent."

As for Affymetrix's proposed construction, it is not adopted because the term "binding agent" does not itself incorporate the concept of specific binding. To the extent that specific binding is required by the patented invention, the phrase "specific for said analyte" in the claim language addresses this issue.

Likewise, Affymetrix's argument that a binding agent must be labeled, raised in its supplemental brief, is rejected because Claim 10 of the '099 patent requires binding agents to be labeled ('099 patent at col. 14:12-15). The doctrine of claim differentiation states that the difference between claims is significant because each claim in a patent is presumptively different in scope. Tandon Corp. v. U.S. Int'l Trade Comm'n, 831 F.2d 1017, 1023 (Fed.Cir.1987). This doctrine is applicable here, as "there is a dispute over whether a limitation found in a dependent claim should be read into an independent claim, and that limitation is the only meaningful difference between the two claims." Wenger Mfg., Inc. v. Coating Mach. Sys., Inc., 239 F.3d 1225, 1233 (Fed.Cir.2001).

For the aforementioned reasons, "binding agent" is 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." This order neither includes nor excludes oligonucleotides and nucleic acids from the definition of "binding agent."

2. "determining the ambient concentrations"

Multilyte proffers the claim construction "deriving an approximation of the amount (*e.g.,* in moles, grams, or molecules) or activity (*e.g.,* in International Units) of a substance in a solution or mixture." Affymetrix argues that this phrase should be construed to mean "calculating a mass, number of molecules, or activity (*e.g.,* grams, moles, International Units) per unit volume (*e.g.,* liter) of fluid to obtain a quantitative, and not qualitative (*e.g.,* yes/no), determination." This order does not adopt either construction. "Determining the ambient concentrations" means "reaching an approximation, rather than an exact calculation, of the amount or activity of a substance in a solution, which is not merely qualitative and is expressed in terms per unit volume, per weight or per parts."

The main points of contention are (1) whether the invention contemplates an exact calculation; (2) whether a quantitative, rather than merely qualitative, analysis is required; FN7 and (3) whether the result must be expressed "per unit volume." This order answers these questions no, yes and no, respectively.

FN7. In the context of immunoassays, a quantitative analysis is distinguished from a qualitative analysis in that the former estimates the *amount,* whereas the latter merely indicates the *presence* or *absence* of the analyte.

With respect to the first disputed aspect of the phrase, this order finds that an exact calculation is not required. The phrase "determining the ambient concentrations" has been treated by the parties as equivalent to "estimating the concentration," a phrase which does not appear in any of the claims allowed to date. This is consistent with the patentee's representations in the prosecution history that the terms "estimating," "determining," and "measuring" were intended to be synonymous (Kappos Decl. Exh. 7 at 8). Indeed, "in a sense all measurements made in science are estimates simply because no measurement is entirely error free" (*ibid.*).

As for whether a qualitative analysis would be sufficient, the prosecution history demonstrated that a key point of novelty was the ability to produce a *quantitative* result. In distinguishing the '099 patent from U.S. Patent No. 4,591,570, ("the Chang patent"), the patentee argued that "Chang discloses an immunoassay device in which an array of antibody coding spots is used for the *qualitative* determination of whether certain antigens are present in a particular sample.... There is no quantitative determination of analyte concentration such as is achievable by the present invention" (Haskett Decl. Exh. L at 13) (emphasis in original). In a later response, the patentee again emphasized that "the assay of Chang is qualitative and provides no disclosure of deducing analyte concentration from the fractional occupancy of binding sites of the binding agent" (Haskett Decl. Exh. M at 9). During reexamination, the method described in UK Patent Application GB 2099578 by Gordon, *et. al.,* (provided as Kappos Supp. Decl. Exh. 32), was also distinguished from the invention in that it would not reveal the "amount or concentration (either in mass or molar units) in the original sample" (Haskett Supp. Decl. Exh. C at 10, n. 15). Thus, merely reaching a qualitative result would be insufficient to "determine the ambient concentrations."

Multilyte argues that a quantitative result in an assay is sometimes translated into a qualitative one, (*i.e.,* if your body temperature exceeds 100 degrees Fahrenheit, you have a fever), so the claim language should not

be limited to situations in which only quantitative determinations are made (Br.13-14). This order does not hold, however, that the *only* result must be a quantitative one. Indeed, the patented assay could produce a quantitative result which is then translated into a qualitative one. For example, a particular hormone concentration might correspond to a diagnosis that a patient either is or is not within the normal, healthy range. But, the prior art already described immunoassays wherein the only result was a qualitative determination of the presence or absence of the analyte. By distinguishing his claimed invention over the prior art, Dr. Ekins disclaimed this type of assay. Lampi Corp. v. Am. Power Prods., Inc., 228 F.3d 1365, 1374 (Fed.Cir.2000).

With respect to whether the result must be expressed "per unit volume," however, nothing in the patents themselves nor their prosecution histories limits the phrase in this manner. This order recognizes that a concentration in solution is typically measured "per unit volume" of fluid, but measurements like "percentage by weight" or "per parts" are not excluded. Finally, Multilyte's proffered claim construction is rejected to the extent that it contemplates a measurement lacking a denominator, such as those already enumerated.

In summary, this order holds that "determining the ambient concentrations" means "reaching an approximation, rather than an exact calculation, of the amount or activity of a substance in a solution, which is not merely qualitative and is expressed in terms per unit volume, per weight or per parts."

3. "loading a plurality of different binding agents ... onto a support means"

The meaning of the phrase "loading a plurality of different binding agents ... onto a support means" is also contested. Multilyte argues that this phrase should be construed to mean "engaging in a process that results in the attachment of two or more different binding agents to a piece of solid material." Affymetrix proffers the narrower interpretation "placing the intact binding agent, *e.g.,* protein or antibody, on a solid support by conventional means known at the time of the invention (*e.g.,* spotting)." This order construes this phrase to mean "immobilizing two or more different binding agents on a solid support, with each location having a single binding agent."

The two primary issues in dispute are (1) whether the binding agent must be "intact" at the time of loading and (2) whether the invention is limited to loading techniques known or conventionally-used. This order finds that the binding agent must be intact when it is loaded onto the solid support, but that the method of loading is not limited to those that were known or conventionally-used at the time of the invention.

By "intact," Affymetrix means that the binding agent should be fully-formed and functional at the time that it is loaded onto the solid support. The Court agrees that there is a conceptual distinction between placing an "intact" molecule onto a solid support and growing or building one thereon. To support its argument that a binding agent need not be "intact" when loaded, Multilyte has offered the analogy of loading a bed into a moving van by first taking it apart, loading the parts, and then re-assembling the bed inside the truck (Br.15). Yet, even this simplified example demonstrates that the process of "loading" is separate from and does not include "assembling."

The intrinsic evidence supports this construction. The claim language reads "loading a plurality of different *binding agents,*" not components or parts thereof. As defined above, "binding agent" means "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." If this molecule is an antibody or a binding protein, Affymetrix

correctly argues that its constituent parts (*i.e.,* individual amino acids), are not capable of binding to an analyte (Opp. 14 n. 13). Thus, the invention would not cover a process of loading individual amino acids onto a solid support. But, assuming *arguendo* that an oligonucleotide is a binding agent, (a possibility which was not explicitly ruled out above), it is possible that individual nucleotides could also be binding agents, in the sense that each one is capable of binding to its complementary base pair. In this sense, the patented invention could theoretically cover a method of determining the ambient concentrations of individual nucleotides in solution, by loading a plurality of single nucleotides onto a solid support.

The prosecution history, however, indicated that "binding agents are loaded onto a support means at a plurality of spaced apart locations, with each location having a *single* binding agent. The term 'loading,' as used in claim 1, cannot reasonably be read to cover a single location having more than one binding agent thereon" (Haskett Decl. Exh. L at 5-6) (emphasis added). Thus, even to the extent that individual nucleotides may be binding agents, the invention does not cover methods that load individual nucleotides one by one onto the same location to create an oligonucleotide, (*i.e.,* growing an oligonucleotide from scratch), as opposed to loading the completed oligonucleotide in a single step.

The second limitation proposed by Affymetrix, namely that the loading method must be spotting or another conventionally-used method, is rejected. The ' 720 patent describes the process of loading as follows:

"The binding agent *may* be immobilized by non-specific adsorption onto the support or by covalent bonding to the support. Techniques for immobilizing binding agents on supports are known in the art ... Such known techniques *can* be used in this invention" ('720 patent at col. 4:17-27) (emphasis added).

Likewise, the '099 patent states that "[t]he binding agents *may* be applied to the support in any of the ways known or conventionally used for coating binding agents onto supports" ('099 patent at col. 7:4-6). While the claim terms are interpreted in light of the specification, this "does not mean that everything expressed in the specification must be read into all the claims." SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1121 (Fed.Cir.1985) (en banc).

The *Kopykake* decision cited by Affymetrix is inapposite. The language in *that* specification regarding "screen printing" explicitly limited the invention to conventional methods. *Compare* Kopykake Enters., Inc. v. The Lucks Co., 264 F.3d 1377, 1380 (Fed.Cir.2001). In contrast, *this* patentee's use of permissive language, like "can" and "may," does not expressly disclaim after-arising technologies for loading binding agents onto a solid support.

The parties also dispute whether the method of combinatorial synthesis used by Affymetrix was known or conventionally-used at the time of the invention. Given the holdings above, however, this is irrelevant.

For the reasons stated above, "loading a plurality of different binding agents ... onto a support means" is construed to mean "immobilizing two or more different binding agents on a solid support, with each location having a single binding agent." While the binding agent must be intact when it is loaded onto the solid support, the method of loading is not limited to those that were known or conventionally-used at the time of the invention.

4. "a plurality of spaced apart small spots"

The final phrase is "a plurality of spaced apart small spots." Multilyte proposes the definition "two or more

areas placed at intervals sufficient to allow useful signals derived from those areas to be determined, and which may be separated by regions from which such signals are not obtained." Affymetrix argues that this phrase should be construed to mean "more than one spot where each individual spot is fully separated from any adjacent spot by a region free of binding agent (*e.g.,* protein or antibody)." This order holds that "a plurality of spaced apart small spots" means "two or more very small areas placed in juxtaposition to one another but at spatially separate points." More specifically, the spaces between these spatially separate points need not be fully vacant, but binding activity in the spaces should be reduced such that the signal-to-noise ratio of each spot is maximized.

This construction is supported by the '099 patent. Therein, the specification explains that using such small amounts of binding agent makes it possible "to place the binding agent required for a single concentration measurement on a very small area of a solid support and hence to place in juxtaposition to one another but at spatially separate points on a single solid support a wide variety of different binding agents specific for different analytes which are or may be present simultaneously in a liquid to be analysed" ('099 patent at col. 3:51-55). The prosecution history lends further support. In describing why the invention was not obvious in light of prior art, the patentee noted that purpose of using spaced apart small spots is that this "maximizes signal-to-noise ratios" (Haskett Decl. Exh. M at 13-14). It was argued that if the invention were indeed obvious, it would have been done already, as improving sensitivity has been a "principal object of immunoassay since the inception of this methodology" (id. at 14).

The principal point of disagreement is whether there must be a region free of binding agent separating the spots. Affymetrix argues that the claims are limited in this way because the inventor clearly envisioned the physical separation between spots to be "desirably, but not necessarily, 2 or 3 times the radius of the spot, or more" ('099 patent at col. 7:23-24). While this may be true, even the language cited by Affymetrix indicates that such a degree of physical separation is not *required*.

Moreover, there is no reason why the areas between spots must be completely vacant, so long as the signal-to-noise ratio of each spot is maximized. Indeed, the patents themselves disclose that certain proteins, such as albumen, may be used as "blocking proteins" that fill in the spaces between spots in order to minimize background noise (id. at col. 10:9-12). As at least one embodiment of the invention explicitly contemplated that the area between the spots would *not* be vacant, this order declines to impose this additional limitation on the claim terms. *Vitronics,* 90 F.3d at 1583 (holding that claim interpretations which read out a preferred embodiment are "rarely, if ever, correct and require highly persuasive evidentiary support").

In conclusion, "a plurality of spaced apart small spots" means "two or more very small areas placed in juxtaposition to one another but at spatially separate points," wherein the spaces between these spatially separate points need not be fully vacant.

CONCLUSION

The Court recognizes that in subsequent proceedings additional claim terms may have to be construed. At a minimum, this will occur before the case goes to the jury. Meanwhile, the foregoing claim-construction rulings shall govern all subsequent proceedings as to these four phrases.

IT IS SO ORDERED.

N.D.Cal.,2005.

Affymetrix, Inc. v. Multilyte Ltd.

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