

Litigation Notes

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AFFYMETRIX v. ILLUMINA: PTO REEXAMINATION OF AFFYMETRIX PATENTS

The PTO ordered a reexamination of four of the five patents at issue in the first of two patent infringement cases brought by Affymetrix against Illumina. Illumina requested reexamination of the fifth patent as well, and this request is still pending. Affymetrix established that Illumina infringes all five of the patents in a jury trial conducted last year before Judge Joseph Farnan of the U.S. District Court in Delaware, but a separate trial on the validity of those patents has not yet occurred and is currently scheduled to begin next month. Illumina's third party request for reexamination, further confirming the failure of settlement talks, appears to reflect Illumina's recognition that its validity arguments will not fare well before the rabidly pro-patent Judge Farnan and that a back-up strategy was called for.

In our analysis, Illumina's validity arguments in support of its reexamination requests were persuasive as to all five of the patents. We think that reexamination will be ordered as to the fifth patent as well, and probably would have been ordered already but for a technical glitch of some sort which required the petition to be resubmitted last month. Judge Farnan will almost certainly have ruled on the validity of the five patents before the PTO completes the reexamination, and if he is true to form he will rule in favor of patent validity on most or all of the patents, but the Federal Circuit will be hard-pressed to affirm in the face of such potent prior art. Moreover, even an affirmance of patent validity will probably be undercut by subsequent PTO action on the patents. Accordingly, we think the only sensible strategy for both sides is to negotiate a settlement, probably for a relatively low price.

We discussed this case in a recent report, cf. *Litigation Notes*, November 9, 2007, in which we cited the difficulty of reaching a negotiated settlement when the judge is biased. We think that Illumina's request for reexamination of the five patents would not have been made if Affymetrix had been realistic about the weakness of its patents and the reasonableness of a royalty rate in light of those weaknesses. We noted further in our previous report that Judge Farnan had asked the jury to determine a reasonable royalty rate without the benefit of any validity evidence whatever, which, in our opinion, is what accounts for the unreasonably high 15% royalty rate (i.e., 15% of total revenues) found by the jury to be a reasonable royalty rate.

Additionally, in that report, we noted that Judge Farnan would probably rule that Illumina would not be permitted to challenge the validity of one of the asserted patents, i.e., U.S. Patent No. 5,795,716, because of the doctrine of assignor estoppel, but we think that he, or the Federal Circuit, will also rule that the jury's infringement verdict must be set aside because of the doctrine of *prosecution history* estoppel. The jury had found that Illumina infringes this patent only by reason of the doctrine of equivalents, and

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Illumina now has a motion to set aside the verdict because the patent was narrowed during prosecution of the patent application and cannot now be broadened under the doctrine of equivalents.

Invalidity arguments against U.S. Patent No. 5,795,716:

Because of the doctrine of assignor estoppel, Illumina probably cannot ask the District Court to rule that the ‘716 patent is invalid, but there is nothing to prevent it from asking the PTO to reexamine the patent in light of its invalidity evidence. The jury found that Illumina infringed Claims 1, 5 and 9 of this patent, and as it happened, Illumina has two anticipatory prior art references, each of which discloses all of the limitations of each of these claims.

We quoted Claim 1 of this patent in our previous report. In general, the claim covers a computer program to determine an unknown base in a nucleic acid sequence, such that probe intensities indicating extent of hybridization are compared in order to make a “base call.” Illumina cites a Ph.D. thesis written by J.K. Elder in 1994 (the precise date in 1994 is unclear from the text) that seemingly contains all of the elements of the claim, including a computer program, “pixel intensities” corresponding to the number of hybridized sequence copies in an array, nucleic acid probes differing from each other by at least a single base, and picking (i.e., comparing, for selection purposes) the strongest string intensity. Accordingly, it argues that the claim is anticipated, and it makes similar arguments with respect to Claims 5 and 9.

Illumina also cites a European patent application submitted by Stephen Fodor (the CEO of Affymetrix) that was published on June 25, 1992, more than two years prior to the October 21, 1994 filing date of ‘716. This patent application had been provided to the patent examiner during prosecution, and the patent examiner concluded that Fodor taught every element of the claims of ‘716 except that the comparison of intensities in Fodor was not used to make a “base call.” Illumina points out that the patent examiner was looking at only one embodiment in the patent when drawing this conclusion, and that in another embodiment, a base call is made directly from the probe intensities. Accordingly, it argues, persuasively, we think, that Fodor anticipates ‘716.

Invalidity arguments against U.S. Patent No. 6,355,432:

The jury found that Illumina infringes Claims 2 and 9 of this patent, but as we stated in our earlier report, the jury’s infringement verdict is clearly wrong in light of the definition of “coding system” adopted by Judge Farnan in his Markman ruling. Judge Farnan had said that the coding system had to be separate from the binding polymer itself, and since Illumina’s coding system is included in the binding polymer (i.e., the DNA), Illumina cannot infringe.

Claims 2 and 9 of the patent are both dependent claims depending on Claim 1, which we quoted in our previous report. The validity arguments that Illumina relies on are based on three prior art documents prepared by Drs. Radomir Crkvenjakov and Radoje Drmanac, including an abstract and a poster submitted at a human genome workshop in Santa Fe on November 3, 1989 and a European patent published on October 17, 1990. The first two items were published more than a year prior to the ‘432 priority date of December 6, 1990 and thus anticipate under 35 U.S.C. §102(b), and the European patent qualifies as anticipatory prior art under 35 U.S.C. §102(a).

Claim 1 of the patent requires a plurality of beads with binding polymers of different sequences attached thereto, plus a coding system permitting identification of the sequences attached to the beads. The Drmanac documents describe “discreet particles,” said to include beads, where each bead carries a unique oligonucleotide of a given length and is labeled in some way for identification purposes. Claim 2 is limited to the situation in which the binding polymer is an oligonucleotide, and Claim 9 covers the

situation in which more than 10,000 oligonucleotide sequences are each attached to a different bead. The petition for reexamination points out that 10,000 is the same as 10^4 , and Drmanac teaches 10^7 in one example and 10^9 in a second example.

Invalidity arguments against U.S. Patent No. 6,399,365:

The PTO has not yet granted reexamination of this patent, but we think it is highly likely that this patent will be added to the mix at the PTO in the near future.

In Illumina's earlier court papers, Illumina was relying on a 1984 British patent issued to Mochida as the primary basis for its obviousness argument against this patent, but in its petition for reexamination its primary prior art reference is an article published by Argonne National Laboratories entitled "SBH and the Integration of Complementary Approaches in the Mapping, Sequencing and Understanding of Complex Genomes," published in January 1993, more than a year before the '365 priority date of June 8, 1994. The jury found that Illumina infringed Claims 36 and 41 of this patent, and Illumina asked the PTO to reexamine those two claims plus Claim 7. Claims 7 and 41 are independent claims, and Claim 36 is a dependent claim based on Claim 7.

Claim 7 covers a probe array deposited on a substrate comprising probes in the array that are biological polymers having a density of more than 100 different biological polymers per cm^2 and also comprising a bar code. Claim 36 adds the limitation that the biological polymers have a density of 1000 different nucleic acids per cm^2 . Claim 41 covers the method of using the probe array that has been described, plus "reading" said bar code, aligning the probe array with a detection system and "detecting a signal from said probe array." The bar code is thought to be the basic invention of the patent.

The Argonne article refers to "spotting" DNA polymers on a nylon membrane. The petition describes "spotting" as one means of immobilizing a biological polymer. The Argonne article states that the pins are .25 mm and the distance between the dots is about 250 μm , resulting in more than 100 different DNA polymers per cm^2 . The article also clearly calls for labeling the plates with a bar code. The petition provides some discussion of whether the bar code must be on the substrate itself with the probe array or whether it may be merely "associated with" the substrate, as in Claim 41, but it identifies prior art passages that cover both alternatives.

Invalidity arguments against U.S. Patent No. 5,545,531:

This patent is the patent covering a chip plate with probe arrays placed in contact with a second surface with wells containing the sample or samples to be tested. The jury found that Illumina infringes Claim 1 and dependent Claim 2, but Illumina has asked the PTO to reexamine all four of the claims in the patent. Illumina relies on a published European patent application by Chetverin et al., PCT Patent Publication WO 93/017126. We discussed this patent application in our previous report, stating that the claims of '126 are so close to '531 as to be indistinguishable to the normal reader, but Judge Farnan denied an Illumina summary judgment motion, stating only that "genuine issues of material fact exist."

Claim 1 teaches a method of making a chip plate comprising providing a body with wells defining spaces, providing a wafer with a plurality of probe arrays on its surface where each probe array has a collection of different probes arranged in a spatially defined manner, and attaching the wafer to the body so that the probe arrays are exposed to the wells.

Chetverin, to us, teaches exactly the same thing, including wells on one surface and a "sheet" made of glass or silica chips with miniature survey arrays, such that the sheet overlays the wells permitting numerous surveys to be conducted simultaneously. Chetverin does not appear to disclose "attaching" the

sheet to the well surface, but Illumina points out that “attach” is defined broadly in the patent to include “even relying on the weight of the body on the wafer to resist the flow of fluids between test wells.” To us, Illumina has a strong case for anticipation with respect to this patent, and in any event the patent certainly appears to be obvious in light of Chetverin.

Invalidity arguments against U.S. Patent No. 6,646,243:

The jury found that Illumina infringes Claims 14, 15 and 35 of this patent. Illumina asked the PTO to reexamine all of the 53 claims in the patent, but mysteriously the PTO concluded that Illumina did not request review of Claims 1-13 or of Claim 51, and it said that accordingly it would not review those claims.

Claim 14 of the patent covers an apparatus for analyzing nucleic acid binding, comprising a substrate with at least 1000 spheres, beads or particles with different species of nucleic acids attached thereto, fluorescently labeled, in a space less than 1 cm², plus a laser energy source to illuminate the fluorescent labels, a detector and a data collection system for storing fluoresced light intensity. Claim 15, a dependent claim, adds the limitation that the substrate comprises wells or the like, and Claim 35 is a method claim basically covering the method of using the disclosed apparatus.

Illumina cites as prior art the same Drmanac documents mentioned above in connection with the ‘432 patent plus an additional article by Drs. Crvenjakov and Drmanac published on January 23, 1991. This article would be too late to qualify as prior art under the effective filing date of March 7, 1990, but Illumina argued that the filing on that date was not enabled, citing an internal memo from an Affymetrix scientist named Michael Pirrung, and that enablement did not occur until 2004. However, the PTO, in accepting the petition for reexamination, said that it rejected Illumina’s argument on enablement, thus leaving the March 7, 1990 priority date in place. Nevertheless, Illumina still has the Drmanac abstract and the poster to rely on as prior art under 35 U.S.C. §102(a).

The petition makes it clear that Drmanac (i.e., the poster and the abstract) disclosed the fluorescent labeling of the DNA to be tested, that Drmanac disclosed lasers as a way to illuminate fluorescent labels on DNA samples, and that Drmanac disclosed fluorescent microscopes and signal detectors and that the signals can be stored digitally as well as on film. To us, Illumina’s argument is persuasive, indicating that the patent is invalid either for anticipation or obviousness.