

Litigation Notes

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SEQUENOM DNA SEQUENCING PATENT LITIGATION

We looked into the patent infringement case filed by **Orchid Cellmark**, a paternity testing company located in Princeton, and its licensee, **Beckman Coulter**, against **Sequenom**. The case was filed on June 5, 2008 and is pending in the U.S. District Court in San Diego, currently assigned to Judge Michael Anello. The case became inactive on November 4, 2008, one day after a court-sponsored settlement conference at which a second settlement conference was scheduled for January 5, 2009.

To us, the inactivity in the case following the settlement conference indicates that settlement efforts are ongoing and that the parties and the court are optimistic enough about the opportunity for settlement to put the case on hold. In our analysis, the critical question is whether either party has a strong enough position in the litigation to dictate the terms of a settlement. We think that the answer to this question is no, since the patents do not appear to be particularly strong, and therefore we think that Sequenom can make respectable arguments on both validity and infringement. Accordingly, the likely outcome of this case, we think, is a settlement in which Sequenom agrees at most to pay a modest royalty.

The patents at issue in this case, U.S. Patent Nos. 6,004,744, 6,537,748 and 5,888,819, cover products and methods for determining a single nucleotide base on a DNA strand using radiolabeled terminator nucleotides such as dideoxynucleotides. The technology has many uses in the field of DNA sequencing, the most valuable of which, we think, is the identification of single nucleotide polymorphisms, or SNPs. The ability to identify SNPs in a human genome is widely regarded as a critical element in the development of personalized medicine.

More specifically, the idea underlying the technology described in the patents is to hybridize a so-called primer (i.e., an oligonucleotide with a nucleotide sequence known to be complementary to a segment of the DNA to be tested) with a single-stranded DNA containing the unidentified nucleotide such that the unidentified nucleotide is first unpaired base downstream of the 3' end of the primer. The next step is to contact the duplex with four possible "terminators," each of which is labeled with a different detectable marker. The terminator attaches itself to the 3' end of the duplex but, by definition, nothing else can attach to the terminator, and therefore the primer cannot extend any further.

Dideoxynucleotides are the primary type of terminator described in the patents, although they say that terminators may be nucleotides, nucleotide analogs, dideoxynucleotides or arabinoside triphosphates. Dideoxynucleotides have a hydrogen atom instead of a hydroxyl group attached to the sugar component of the nucleotide, and since the hydroxyl group is needed for attachment of the next nucleotide in chain elongation, attachment of a dideoxynucleotide effectively terminates the elongation process.

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There are four dideoxynucleotides, each corresponding to one of the four classic nucleotides of DNA. The four dideoxynucleotides are dideoxyadenosine triphosphate, dideoxycytosine triphosphate, dideoxyguanosine triphosphate and dideoxythymidine triphosphate. The patent teaches that these dideoxynucleotides can each be labeled with a different marker, or the same marker can be used in four different batches, and the unidentified nucleotide will be complementary to whichever dideoxynucleotide attaches to the duplex at the 3' end.

The inventors listed in the three patents are Philip Goelet, Michael Knapp and Stephen Anderson. Goelet, as we understand it, was the founder of Molecular Tool, Inc., the assignee of the patents. Molecular Tool, established in 1989, was acquired by an Orchid subsidiary in 1996. Cellmark, in turn, a forensic and paternity testing company, was a division of AstraZeneca that was sold to Orchid in 2001. Goelet is also a principal of a private equity firm named Red Abbey Partners. From our limited research on the question, it does seem that Goelet and his associates were the first to describe this particular primer extension technique for the identification of SNPs.

The patent claims are limited to the primer extension approach described above, but within that category the patents have broad claims that appear to cover the category pretty well. For example, Claim 1 of the '744 patent, which we regard as fairly broad, reads as follows:

1. A reagent composition which comprises an aqueous carrier, a primer nucleic acid molecule, a template nucleic acid of interest hybridized thereto, and an admixture of at least two different terminators of a nucleic acid template-dependent, primer extension reaction, each of the terminators being capable of specifically terminating an extension reaction of said primer hybridized to said template nucleic acid molecule of interest in a manner strictly dependent on the identity of the unpaired nucleotide base in said template nucleic acid molecule of interest immediately adjacent to, and downstream of, the 3' end of said primer, and at least one of the terminators being labeled with a detectable marker, and wherein said reagent composition lacks dATP, dCTP, dGTP, and dTTP.

dATP, dCTP, dGTP and dTTP are deoxynucleotide triphosphates, collectively referred to as dNTP. They are the basic reagents used in PCR when continuous chain elongation is sought. The terminators, i.e., the dideoxynucleotide triphosphates, are designated as ddATP, ddCTP, ddGTP and ddTTP. All of the claims in the patents have the limitation that the reagent composition must lack the dNTPs.

The Sequenom product accused of infringement in the case is something that the company calls MassARRAY*®*iPLEX, which it uses for SNP genotyping. The system uses PCR to amplify the DNA segment of interest, followed by the single base extension process described above. However, instead of using labels and markers to detect which dideoxynucleotide attaches to the duplex, it uses mass spectrometry, which it calls MALDI TOF MS (i.e., "Matrix-Assisted UV-Laser Desorption/Ionization Time of Flight Mass Spectrometry"). It is the source of a "substantial portion" of Sequenom's revenues.

The use of mass spectrometry to identify SNPs is described in three patents owned by Sequenom, i.e., US. Patent Nos. 7,419,787, 6,300,076 and 6,500,621. We have not yet undertaken to determine whether this patent position would permit Sequenom to control the field of SNP identification by mass spectrometry, but the patents do impress us as substantial contributions to the art. These patents were asserted against Ibis Biosciences, a subsidiary of **Isis Pharmaceuticals**, in a case filed on October 30, 2008. Ironically, this case became inactive on November 5, 2008, one day after the Beckman Coulter case became inactive.

According to these three patents, mass spectrometry has been used extensively in the biosciences as a means to identify organic molecules, but their use in identification of nucleic acids has been difficult because they are “polar” and hence difficult to “volatilize.” The basic technique of mass spectrometry is to ionize the molecules of interest, then to volatilize them by laser energy and then by making them “fly” in a combination of electric and magnetic fields. The trajectory of the molecules depends on their mass and charge, which can be detected and recorded in a computer, facilitating automated processing.

The process for SNP identification is described a bit more in one of the embodiments of the invention described in the patents. It says that a primer with 3’ terminal base complementarity to a mutant or normal allele is hybridized to the target, and then, using an appropriate polymerase, nucleoside triphosphates are used to extend the primer, and the identity of the added nucleoside can be established by molecular weight shift as determined by mass spectrometry.

The advantages of this process, according to the patents, is that the entire procedure, including nucleic acid isolation, amplification and identification by mass spectrometry can be completed in about 2-3 hours, and since the process employs rigorous controls, it eliminates the false negatives and false positives that result from procedures involving labeling and label detection. It is unclear to us how, under this process, nucleoside triphosphates can be used to extend the duplex by only a single base, but we think the patents may assume that a person of ordinary skill would use a terminator instead of a regular dNTP if only a single base was to be added to the duplex.

As for the arguments that Sequenom can make in settlement negotiations, it appears to us that Sequenom has an effective noninfringement argument against the three patents currently asserted against it, since every claim in the three patents includes the limitation that the terminators must be labeled with a detectable marker. From the above description of mass spectrometry, we do not believe that detectable markers are used, and in fact, the ability to dispense with labeling and label detection is regarded as one of the major benefits of using mass spectrometry to identify the SNP.

The problem with this noninfringement argument is that the specification of the Orchid patents clearly includes mass spectrometry as one of the possible methods for identification of the SNP. Accordingly, Orchid and Beckman may file a continuing application at the PTO to secure coverage of mass spectrometry as one of the many means of identifying the single base extension. They may have difficulty securing such coverage, however, since the process is tricky and the patents do not seriously explain how to do it. Orchid and Beckman would have to argue that the mass spectrometry techniques were well-known in the prior art, which, if true, would raise a question about the validity of the three Sequenom patents asserted against the Isis subsidiary.

We also think that a good argument is available that the invention disclosed in the asserted Orchid/Beckman patents was obvious and that therefore the patents are invalid. The technology of attaching a primer to a single stranded DNA and then extending the duplex in the presence of a polymerase was well-known prior to the filing date of these patents, and so too was the technology of using dideoxynucleotides to terminate duplex extension. We think that these ideas are at least as old as the invention of PCR by Kary Mullis, which goes back to the early 1980s. In fact, PCR itself seems to incorporate the basic ideas of the patents other than labeling the dideoxynucleotides, and we think that the concept of labeling nucleotides and dideoxynucleotides with detectable markers was well-known long before these patents came along.